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ORIGINAL ARTICLE

Epidemic Retinitis

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ABSTRACT

Purpose: To study demography, seasonal variation, clinical presentation, and treatment outcome of “retinitis post febrile illness.” (RpFI)

Method: Case records of patients diagnosed as RpFI, from July 2009 to May 2017 were studied retrospectively. Patients with complete follow up were evaluated for treatment and visual outcomes.

Results: Two hundred and five eyes of 119 patients were studied. The peak incidence of RpFI was from November to March each year. Diagnosis of fever largely remained unknown. Chikungunya IgM, Dengue IgM, and Weil–Felix test was positive in 22.22%, 15.38%, and 39.75%, respectively, in investigated cases. The mean visual acuity at presentation and at resolution was 20/63 and 20/32, respectively, in 122 eyes with complete follow up.

Conclusion: We suggest a term “Epidemic Retinitis” for RpFI due to its seasonal variation and to differentiate it from other sporadic forms of retinitis. Although RpFI has aggressive presentation, it resolves over 3–4 months and the overall visual outcome is satisfactory.

Keywords: Chikungunya, dengue, epidemic retinitis, multifocal retinitis, retinitis post febrile illness, rickettsia, seasonal variation

Uveitis post febrile illness has been described in many epidemics like Leptospirosis, Chickungunya, Dengue, West Nile Virus (WNV), Rickettsiosis and recently even in Ebola.¹–⁶ Retinitis has been reported in many of these conditions.⁷,⁸ This retinitis is generally multifocal, cotton wool spot-like lesions localized in the posterior pole and around the disc and are associated with vitritis. Few of these outbreaks are known to repeat each year in tropical countries like India. Causative organism could be different for different epidemics but manifestation could be same in the form of retinitis. Systemic or local steroids are the mainstay therapy for these conditions. Seasonal variation, diverse etiologies and visual outcomes with different treatment modalities for retinitis post febrile illness (RpFI) has not been studied in a large cohort. Herein, we report demography, seasonal variation, clinical presentation, course of the disease and treatment outcomes of RpFI in our population.

SUBJECTS AND METHODS

This is a retrospective, observational study of patients presenting to a single eye care institution in south India from July 2009 to May 2017. The study was approved by internal review board and adhered to the declarations of Helsinki. All patients with case records having a diagnosis of RpFI were reviewed.

The diagnosis of RpFI was based on history and clinical examination. A history of recent fever followed by ocular symptoms within 1–2 months, with diagnosis of or suspicion of dengue, chikungunya, rickettsia, west-nile virus, typhoid, presumed viral fever, and fever of unknown origin were included whereas...
patients with diagnosis of fever due to abscess or localized infection elsewhere in the body, fever in case of known autoimmune disease (e.g., SLE) were excluded. Criteria for clinical examination included presence of focal or multifocal cotton wool spot-like (CWS) retinitis lesions around the disc or in the posterior pole with presence of vitritis and after exclusion of following conditions clinically and/or with appropriate investigations where needed: hypertensive and diabetic retinopathy, systemic autoimmune diseases (SLE), toxoplasmosis, acute retinal necrosis, CMV retinitis, syphilis, endogenous endophthalmitis, and retinitis in immunocompromised patients.

Demographic details, month of presentation, follow up duration, history of present illness, best corrected visual acuity (BCVA) at the presentation and at the resolution, slit-lamp examination, investigations, and treatment details were studied. To study demographics, month of presentation and history of present illness all the patients were included in the study and for evaluation of treatment outcome patients with complete follow up till resolution were included. The condition was considered resolved when BCVA was noted stable in at least 2 subsequent visits, absence of macular edema clinically or on Optical Coherence Tomography (OCT), resolved disc edema and fading of CWS-like retinitis lesions. Patients who received similar treatment were grouped together. Visual recovery with different treatment modalities were studied for the patients presented with BCVA 20/50 or worse and completed follow up until resolution. Being a retrospective study no standard investigation or treatment protocol was followed.

STATISTICAL ANALYSIS

The data was entered in Microsoft Excel 2013 for Windows and analyzed using SPSS 22.0 for Windows (IBM). Normality was tested using the Shapiro–Wilk test. For comparison of means between multiple independent groups the one-way ANOVA test was used with the Tukey test for post hoc analysis.

RESULTS

Two hundred and five eyes of 119 patients were studied. Eighty-seven patients had bilateral presentation. Mean age of presentation was 37.74 years (range 6–77 y). Seventy-three were male, 46 were females, and 6 were pregnant at presentation. Three patients gave history of tick bite (a goat tick, a dog tick and an unknown tick). No patient gave history of previous similar episode. Each year the RpFI started in month of August and ended in month of May of subsequent year. The maximum number of cases were seen between November to March (Figure 1). Patients developed ocular symptoms after a latent period of 4 days to 8 weeks of the fever (mean 18.36 days). Thirty-five patients had history of skin rash (Figure 2) following fever and 26 patients had joint pain. Following diagnosis was made for the fever by their treating physicians: typhoid (n = 15), measles (n = 1), dengue (n = 7), chikungunya (n = 2), viral thrombocytopenic fever (n = 3), viral meningo-encephalitis (n = 2), malaria (n = 3), suspected rickettsial (n = 3), and leptospiral fever (n = 1). But, in most of the patients the diagnosis of fever remained unknown and was presumed to be of unknown viral etiology. Treatment records for fever were available only for few patients. Most of them received cephalosporins, short courses of systemic steroids and i.v. fluids (systemic steroids (n = 7), systemic cephalosporins (n = 10), anti-tubercular treatment (n = 1), acyclovir (n = 1), doxycyclin (n = 3), azithromycin (n = 6), amikacin (n = 1), ayurvedic medicine (n = 1), artesunate (n = 2), and i.v. fluids (n = 8).

The mean presenting BCVA was 20/60 (range: 20/20 to Hand Motions). Eighty-five eyes (41.46%) had best corrected visual acuity (BCVA) less than 20/200 at presentation. Intraocular pressure was normal in all eyes except 2 steroid responders. Thirty-seven eyes had fine keratic precipitates (KPs) and mild to moderate anterior chamber reaction. Small granulomatous KPs were seen only in 6 eyes. Posterior synechia were seen rarely and no iris nodules were observed.

FIGURE 1. A month wise graphical representation (from July 2009 to May 2017) shows RpFI gradually starts in the month of August, peaks between November and March then falls rapidly and disappears in month of June.
Vitreous haze was grade 2 or less in all eyes. Hundred and thirteen eyes (55.12%) had macular edema. Only 3 eyes had focal retinitis whereas rest all eyes had multiple cotton-wool-spot like retinitis lesions at posterior pole or around the disc with or without disc edema and/or few retinal hemorrhages. The size of CWS-like lesions ranged from ½ disc diameter (DD) to 3 DD. Ten eyes developed “macular star” during resolution of macular edema. During follow up migration of retinal lesions toward macula was noted in few cases (Figure 3a, 3b). Fundus fluorescein angiography (FFA) (39 eyes) revealed early hypofluorescence corresponding to retinitis patches which gradually turned hyperfluorescent at border of the retinitis lesions. Staining with mild leakage from adjacent retinal vessels was also noted which suggested presence of subclinical retinal vasculitis (Figure 3c). OCT (127 eyes) showed increased inner retinal reflectivity with after-shadowing corresponding to the area of retinal lesions and intraretinal hyper-reflective dots suggestive of hard exudates (Figure 3d). In all cases, resolution of the disease was noted over 2–4 months after treatment. One case showed resolution over 5 months without any treatment. CWS-like retinitis lesions took more time to fade away but invariably resolved completely without formation of pigmented scar. Inflammatory neovascularization elsewhere (NVE) developed without evidence of capillary nonperfusion areas on the FFA in 3 eyes. Two of these cases also had associated diabetes but no diabetic retinopathy at presentation.

Being a retrospective study, it was not possible to follow standard investigation and treatment protocol. Most of our cases tested positive for Weil–Felix test (WFT) but the gold standard test for rickettsia (immuno-fluorescence assay – IFA) was positive (spotted fever and typhus fever group at 1:128 dilution) only in 1 out of 3 patients. Scrub typhus IgM by ELISA and PCR was negative in all tested cases (n = 4). WNV serology (IgM ELISA, Sandwich ELISA) and aqueous (RT-LAMP assay) done in nine patients, tested negative (Table 1). Although IgG titers for Mumps, Measles and Rubella are nonspecific, in a pregnant female, rubella IgG titer was found to be significantly high (> 350). Interestingly multiple tests were positive in some individuals (Table 2). Out of 13 cases of thrombocytopenia, only 3 were...
suspected for dengue fever by their physician. AC Tap for PCR based detection of viruses (HSV<sup>n</sup> = 5, VZV<sup>n</sup> = 5, CMV<sup>n</sup> = 6, chikungunya<sup>n</sup> = 2, dengue<sup>n</sup> = 1, WNV<sup>n</sup> = 9), and PCR for scrub typhus (<sup>n</sup> = 4) was negative in all tested cases.

Treatment and visual outcome was studied in patients with complete follow up with resolution of the disease (<sup>n</sup> = 70). Systemic steroid was mainstay therapy in most of the patients. One case received no treatment at all and his vision improved spontaneously from 20/200 to 20/30 over 5 months. Majority of patients received oral doxycycline (<sup>n</sup> = 46) and/or aciclovir or valacyclovir (<sup>n</sup> = 30), started empirically while investigations were awaited. Five patients received intravenous methylprednisolone (IVMP), 11 eyes received posterior subtenon’s injection (PST), 2 eyes received intravitreal triamcinolone (IVTA), 2 eyes received both PST and IVTA and 20 eyes were treated with intravitreal anti-VEGF injections (bevacizumab: 14, ranibizumab: 6).

The mean BCVA in 122 eyes with complete follow up, improved from 20/63 at the presentation to 20/32 at the resolution. Visual recovery with different treatment modalities was studied for 93 eyes with visual acuity 20/50 or worse and with complete follow up (Table 3, 4). Presenting BCVA in “Anti-VEGF + steroid” group was poorer despite this they improved equally compared to other groups, although the difference was not statistically significant. Comparing group 1 (doxycycline + antiviral + oral steroids) and 2 (doxycycline + oral steroids) (Table 3), it was clear that addition of antiviral medication made no significant difference in terms of visual gain, neither avoiding antibiotics and antivirals both as in the group 3

### TABLE 1. Investigations.

<table>
<thead>
<tr>
<th></th>
<th>Chik IgM</th>
<th>Deng IgM</th>
<th>Deng IgG</th>
<th>NS1</th>
<th>Ox 2</th>
<th>Ox 19</th>
<th>Ox K</th>
<th>Rickett IFA</th>
<th>Scrub Typhus IgM-PCR</th>
<th>WNV*</th>
<th>WIDAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases tested</td>
<td>6 (22.22%)</td>
<td>2 (15.38%)</td>
<td>15 (88.23%)</td>
<td>0</td>
<td>25 (30.12%)</td>
<td>16 (19.27%)</td>
<td>3</td>
<td>1  (0.03%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>7</td>
</tr>
<tr>
<td>Positive investigation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33 (39.75%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of cases tested</td>
<td>27</td>
<td>13</td>
<td>17</td>
<td>6</td>
<td>83</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Serology (IgM ELISA, Sandwich ELISA) and aqueous (RT-LAMP assay)

Chik: Chikungunya, Deng: Dengue, WFT: Weil Felix Test, Rickett: Rickettsia, WNV: West Nile Virus

### TABLE 2. Multi test positivity.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Chik IgM</th>
<th>Deng IgG</th>
<th>Rickett IFA</th>
<th>WFT</th>
<th>ANA</th>
<th>WIDAL</th>
<th>Toxo IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>


### TABLE 3. Comparison of visual gain with different treatment modalities.

<table>
<thead>
<tr>
<th>Grps.</th>
<th>Treatment modalities</th>
<th>No. Of eyes</th>
<th>Positive investigation: number of patients</th>
<th>Mean BCVA @ Prtn</th>
<th>Mean BCVA @ resolution</th>
<th>Mean Line gain on Snellen&lt;sup&gt;23&lt;/sup&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Doxy + Antiviral + oral steroids</td>
<td>33</td>
<td>Chick IgM:2 DENG:8 WFT:8 WIDAL:2</td>
<td>20/160</td>
<td>20/40</td>
<td>9.6</td>
<td>0.613</td>
</tr>
<tr>
<td>2</td>
<td>Doxy + oral steroids</td>
<td>12</td>
<td>Deng IgG: 1 WFT: 4 WIDAL: 2</td>
<td>20/160</td>
<td>20/30</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No Doxy/Antiviral but oral steroids and allied treatment*</td>
<td>24</td>
<td>Deng IgG: 5 WFT: 5 WIDAL: 1</td>
<td>20/200</td>
<td>20/40</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Anti VEGF + oral steroids</td>
<td>10</td>
<td>Deng IgG: 3 WFT: 4 WIDAL: 1</td>
<td>20/250</td>
<td>20/40</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>

Chik: Chikungunya, Deng: Dengue, WFT: Weil Felix Test, Anti VEGF: Bevacizumab or Ranibizumab, Doxy: Doxycycline, Antiviral: Acyclovir or Valacyclovir, BCVA: Best corrected visual acuity, @ Prtn: at presentation,

* Posterior Subtenon’s injection or intravitreal triamcinolone or Anti VEGFs or i.v. methylprednisolone or combined treatment
TABLE 4. Steroid versus no steroids.

<table>
<thead>
<tr>
<th>Grps.</th>
<th>Treatment modalities</th>
<th>No. Of eyes</th>
<th>Positive investigation: number of patients</th>
<th>Mean BCVA @ Prtn</th>
<th>Mean BCVA @ resolution</th>
<th>Mean Line gain on Snellen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral Steroids</td>
<td>5</td>
<td>Deng IgG: 1</td>
<td>20/80</td>
<td>20/30</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>PST + Oral steroids</td>
<td>4</td>
<td>Rubella IgG: 1</td>
<td>20/800</td>
<td>20/100</td>
<td>9.5</td>
</tr>
<tr>
<td>3</td>
<td>No Steroids</td>
<td>5 (1 + 3 + 1)</td>
<td>Deng IgG: 1, WFT: 1</td>
<td>20/250</td>
<td>20/40</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Doxy</td>
<td>1</td>
<td>WFT, Rubella IgG: 1</td>
<td>20/80</td>
<td>20/20</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Anti VEGF</td>
<td>3</td>
<td>Deng IgG: 1</td>
<td>20/200</td>
<td>20/40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Nil</td>
<td>1</td>
<td></td>
<td>20/200</td>
<td>20/30</td>
<td>13</td>
</tr>
</tbody>
</table>

Deng: Dengue, WFT: Weil Felix Test, PST: Posterior Subtenon’s injection, Anti VEGF: Bevacizumab or Ranibizumab, Doxy: Doxycycline, BCVA: Best corrected visual acuity, @ Prtn: at presentation.

(No antibiotic and antiviral) showed any statistically significant difference. Comparison between patients who received “steroids only” treatment and “no steroid” treatment was as shown in Table 4. Due to small numbers, statistical significance was not evaluated. “No steroids” group (Group 3 – Table 4) gain relatively more lines at the resolution, whereas “PST + oral steroid” group (Group 2 – Table 4) gain less. Perhaps, presenting visual acuity was significantly poorer in the group 2 compared to other groups (Table 4).

Complications such as retinal neovascular elsewhere was noted in 3 eyes, vitreous hemorrhage in 1 and total disc pallor in 3 eyes. No patient had relapse of inflammation during entire follow up period.

DISCUSSION

This is a large study from Indian subcontinent which addresses the question of seasonal variation, course of the disease, varied etiology and treatment outcomes with different treatment modalities in RpFI. Numerous causes have been reported for RpFI viz. chickungunya, dengue, typhoid, malaria, WNV fever, rickettsiosis, bartonellosis, lyme’s disease, rift valley fever etc.4,7–9 A battery of specific investigations is needed to pinpoint the cause when work up for preceding fever is poorly done. Often it is not possible to do all serological investigations due to financial constraints and unavailability of gold standard test in Indian scenario. Contemporary epidemic in tropical countries may give clue toward the etiology of RpFI. Figure 1 shows that RpFI was prevalent in winter season (November–March) in our province, hence contemporary epidemics in the community in winter season should be studied to find region specific common cause of RpFI. History of travel to such endemic areas during the outbreak just before onset of fever is important. Chikungunya, dengue, WNV are mosquito-borne diseases, but for rickettsiosis history of tick or mite bite is important as elicited in 2 of our patients (a dog tick and a sheep tick). In most of the cases diagnosis of fever was not made by their physician and was presumed to be viral, but many cases were diagnosed to have typhoid fever (n = 12). Various forms of uveitis post typhoid fever and post typhoid vaccination has been reported10,11 but RpFI due to typhoid has been scarcely reported.12 Physician should be aware of RpFI and close interaction between ophthalmologist and internist is needed for better understanding of the etiology.

Standard investigation protocol was not followed in our study and investigations done were a mixture of physician trying to find a cause for fever and ophthalmologist trying to rule out a systemic disease. Although chickenpox and mumps causing retinitis and neuro-retinitis has been described in the literature12,13,14,15 none of our patient presented with history of chicken pox or mumps which is an obvious clinical diagnosis. Rather a patient was diagnosed as measles by her physician and presented with RpFI as reported by Neppert and Bonamour et al.16,17 Rubella retinopathy is known to occur in younger children but little is known about its presentation in adults. Damasceno et al. have reported a case of retinitis and vasculitis after a febrile illness, proven to be “rubella in adult.”18 All our patients who underwent serology for Mumps, Measles, Rubella (MMR) tested negative for IgM and positive for IgG including significantly high titers of rubella IgG in a pregnant lady. Taking into consideration that patients presented to us after a latent period of around 2 weeks, possibility of receding IgM antibody titers cannot be ignored. Same is true for other etiologies such as dengue and chikungunya. WNV retinitis has been well described by Shivakumar et al.4 We noted similar clinical presentation of the disease in our patients as well,
unfortunately only nine patients were evaluated for WNV in our series and all tested negative for same (Table 1). Most of our cases (almost 40%) tested positive for WFT, some of them also had cross reaction with other serological tests Viz. dengue, Widal and Toxoplasma IgG. WFT, although not a gold standard test for diagnosis of rickettsial diseases, its value has been proven in a few Indian studies. 

Presumed rickettsial retinitis based on WFT in Indian scenario has been recently reported. Confirmed rickettsial diagnosis (spotted fever group) using gold standard IFA, was made only in 1 patient and interestingly the patient also had positive dengue IgG titers. Our study has brought out the issue of diagnostic difficulties due to cross-reaction between various serological tests. Attempts to isolate organism from ocular fluid were also failed in our series. Speculations of CWS-like retinitis lesions actually harboring active organism needs to be addressed by using molecular diagnostics of ocular fluid for all suspected organisms or perhaps using “next-generation sequencing.” Interestingly hypertensive uveitis was not seen in this series. This may help exclude viruses responsible for uveitis with high IOP.

A significant number of patients in our series had macular edema which quickly responded to treatment and did not recur. Exceptions were diabetic and older patients. Resolution of retinitis without formation of pigmented scars suggested predominantly inner retinal involvement. Development of new vessels in the absence of capillary nonperfusion may suggest increase levels of VEGFs due to inflammation in RpFI.

As a rule, RpFI resolved in all cases without any relapses but visual prognosis varied depending on macular ischemic damage and optic nerve involvement. Although we did not find statistically significant difference between different treatment modalities, despite relatively poorer presenting visual acuity “anti-VEGF + steroids” group fared better compared to other groups (Table 3). Acceptable visual gain in “No steroid” group in our study may encourage treating RpFI by alternative therapy such as intravitreal anti-VEGFs.

Bilaterality of RpFI (73% cases), average 18 days of latent period, almost symmetrical CWS-like retinitis lesions mostly around the disc and at posterior pole and favorable response to steroids may suggest RpFI is a para-infectious process. Its seasonal variation (prevalence in winter), widespread occurrence in the community and possible causes like chikungunya, dengue, WNV and rickettsia encouraged us to use a term “Epidemic Retinitis” to differentiate this entity from sporadic forms of retinitis of other etiologies. In conclusion, Epidemic Retinitis has an acute onset, nonrecurrent course and has overall good visual prognosis.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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