Special Focus, Retina, Original Article

Epidemic retinitis - Factors associated with poor visual outcomes

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Purpose: To identify factors other than macular edema and retinitis location responsible for poor visual outcomes in epidemic retinitis (ER). **Methods:** A retrospective, observational, comparative study. Eyes with corrected distant visual acuity (CDVA) 20/200 or worse at resolution formed Group A. Eyes with central macular thickness (CMT) 600 µm or worse and retinitis within 1500 µm to foveal center at the presentation, but improved to CDVA 20/200 or better at the resolution formed Group B. The patient's history, clinical presentation, imaging, and treatment outcomes were studied and the factors responsible for the final visual outcomes were compared in both groups. **Results:** Groups A and B included 25 eyes each. The mean CDVA at the presentation was 20/400 (range: 20/125–20000) and 20/320 (range: 20/80–20000), and mean CMT at the presentation was 948.5 µm (range: 520–1553) and 912.2 µm (range: 615–1250) in Groups A and B, respectively. All eyes except 1 (Group A) had retinitis lesions within 1500 µm of foveal center. The mean CDVA at the resolution was 20/400 (range: 20/200–20/20000) and 20/40 (range: 20/20–20/80) in Groups A and B, respectively. Older age, male gender, diabetic status, delayed presentation, poor presenting CDVA, bilaterality, presence of keratic precipitates, disk pallor, retinal thinning, and subfoveal deposits had a statistically significant association, whereas the absence of skin rash, ellipsoid zone loss, negative WIDAL, Weil-Felix test, and delayed doxycycline therapy or use of steroids without doxycycline had a statistically insignificant association with poor visual outcomes. **Conclusion:** Apart from presenting CMT and location of retinitis, multiple demographic, clinical, and imaging factors can be implicated for poor visual outcomes.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1153_21

Quick Response Code:

Key words: Doxycycline, epidemic retinitis, post-fever retinitis, treatment, visual outcomes

Epidemic retinitis (ER) or post-fever retinitis comprises a uveitic entity with a similar morphological pattern and course of the disease but different etiologies such as rickettsia, typhoid, dengue, chikungunya, and West Nile virus.[1,2] As a rule, there is a recent history of fever with or without joint pain and skin rash. In most cases, the diagnosis of the fever remains uncertain due to non-specific systemic manifestations or lack of gold-standard investigations. Although the ocular presentation is acute with significant, often bilateral visual loss due to severe macular edema and retinitis, the visual outcome is good in a majority of cases.[3] The factors responsible for poor visual outcomes such as retinal neovascularization with vitreous hemorrhage, maculopathy, retinal thinning, macular ischemia have been reported in a few case reports and small case series.[4-6]

In a recently published series of 16 patients, certain optical coherence tomography (OCT) scan biomarkers were predicted to be responsible for poor visual outcomes.[7] Macular involvement in ER is common and as expected is directly associated with visual outcomes. Comprehensive comparative systematic evaluation of causes for unsatisfactory treatment outcomes in a larger series has not been reported in any studies on ER. Our study investigates factors other than presenting macular edema and retinitis which can be associated with poor visual outcomes in ER.

Methods

This is a retrospective, observational, comparative study of the patient diagnosed as ER presented to a single tertiary care eye hospital in South India. The study was approved by the internal review board and adhered to the Declarations of Helsinki. Patients with a history of recent fever presented with focal or multifocal "cotton wool spot-like" retinitis lesions as described previously were diagnosed as cases of ER.[1] The electronic medical record (EMR) data of those patients were reviewed from January 2013 to 2021.

The eyes with corrected distant visual acuity (CDVA) 20/200 or worse at the resolution of ER were isolated to form Group A. After studying the presenting retinitis pattern and macular edema on fundus photo and Spectral-domain (SD)-OCT Heidelberg SpectralisTM) in Group A, the remaining eyes with CDVA 20/200 or better at the resolution were evaluated for the same. An equal number of consecutive eyes from the remaining sample with a central macular thickness (CMT) worse than 600 µm and retinitis lesions within 1500 µm to foveal center at the presentation were isolated to form Group B for the comparative study.

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Received: 09-May-2021 Revision: 20-Aug-2021
Accepted: 16-Oct-2021 Published: 25-Feb-2022

Cite this article as: Kawali A, Sanjay S, Mahendradas P, Mohan A, Shetty B. Epidemic retinitis - Factors associated with poor visual outcomes. Indian J Ophthalmol 2022;70:897-901.

To study the location of retinitis lesions, the foveal center was detected on an SD-OCT scan image using the marker. A straight-line measuring 1500 μm was stretched from the foveal center, along the plane of the detached retina toward the retinitis lesion, which was visible as indistinct layers with after shadowing [Fig. 1a].

The cases with incomplete follow-up and the eyes with media haze or pre-existing disease contributing to poor visual acuity were excluded. The resolution of ER was defined as the absence of macular edema and retinitis lesions as recorded clinically and/or on OCT scan and wide-field fundus photograph. The patient's history of the present illness, systemic and ocular clinical examination, ocular imaging studies, laboratory investigations, treatment, and visual outcomes were studied for all patients.

Statistical analysis

All data were entered in Microsoft Excel 365 and analyzed using IBM SPSS v27.0. Data were checked for normality using the Shapiro-Wilk test. The comparison of the means was done using the Mann-Whitney U test and the proportions were compared using the Chi-square test. A *P* value of less than 0.05 was considered significant.

Results

One hundred and eighty-one patients were diagnosed with ER in 8 years. Sixty-two patients who had incomplete follow-up and/or eyes with media haze and/or pre-existing disease were excluded from the study. Among the remaining 183 eyes of the 119 patients, 25 eyes (13.6%) of 20 patients had final CDVA 20/200 or worse and they formed Group A. Twenty-five eyes of 23 patients with final CDVA 20/200 or better formed Group B. All patients had a history of fever for which the etiological diagnosis was made by their primary physician only in a few cases (n = 18): Group A: typhoid (n = 4), chikungunya (n = 1), dengue (n = 2), viral fever (n = 1), malaria (n = 1), viral meningitis (2); and Group B: typhoid (n = 2), dengue (n = 2), viral fever (n = 3).

Demography, history, and clinical data are shown in Table 1. Diabetics, males, and slightly older patients were seen more frequently in Group A. Only 1 patient was hypertensive from each group and the hypertension was under control. Five out of 7 and 1 out of 1 had uncontrolled diabetes (hemoglobin A1c [HbA1c] greater than 7%) in Groups A and B, respectively. A history of joint pain and skin rash during and after the fever were present in more patients in Group B although not statistically significant. Latent period, first ophthalmic consultation, and tertiary eye care referral were delayed in Group A. Keratic precipitates (KPs-non-granulomatous) were seen more frequently in Group A. All patients had focal or multifocal retinitis with macular edema. The disc pallor was found in significantly more cases in Group A at the resolution.

In Group A, the SD-OCT scan was available at the presentation in 17 eyes. The mean central macular thickness (CMT) was 948.5 μm (range: 520–1553 μm) and retinitis lesions within 1500 μm of the foveal center were seen in 16 eyes. In Group B, the mean CMT was 912.2 μm (range: 615–1250 μm) (n = 25) and all eyes had retinitis lesions within 1500 μm of the foveal center but all improved to CDVA 20/200 or better (n = 25). The imaging findings are shown in Table 2. The SD-OCT scan at the resolution was available for 23 eyes in Group A and for 18 eyes in Group B. Retinal thinning, indistinct retinal layers (smudge effect) [Fig. 1b], and subfoveal deposits were statistically significant in Group A. More number of retinitis lesions, vasculitic leakage, occlusion of second-order vessels [Fig. 2a], and neovascularization on fundus fluorescein angiography (FA) was seen frequently in Group A but was statistically insignificant. The active retinitis lesions showed hypofluorescence at an early stage and staining of borders in the late phase on FA. After resolution, partial reperfusion of occluded second-order vessels was seen but capillary defects at the site of retinitis lesions persisted [Fig. 2b].

The patient's laboratory investigations and treatment are shown in Table 3. Most of the patients in Group B tested positive for the WIDAL and Weil-Felix Test and more than 50% received oral doxycycline within 2 weeks of ocular

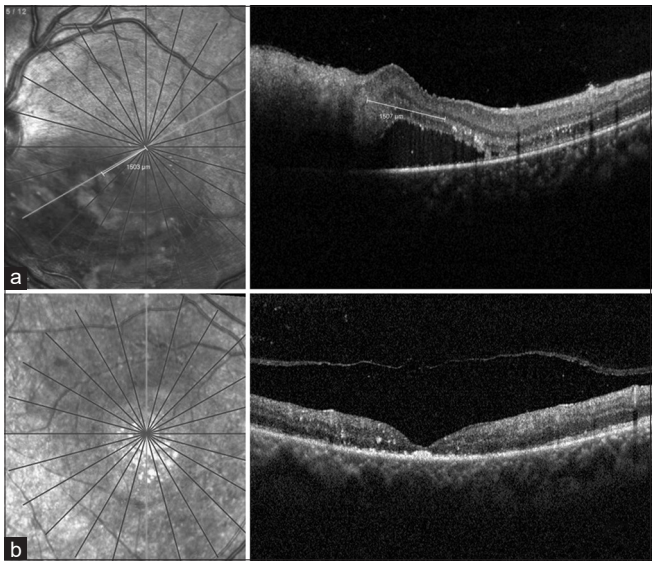

Figure 1: OCT scan at the presentation in an 11-year-old female from Group B shows indistinct layers of retina at the site of retinitis lesions with after shadowing and subretinal fluid and hard exudates in the outer nuclear layer. The nearest retinitis lesion is falling within 1500 μm of the center of the fovea. (a) OCT scan at the resolution in a 48-year-old patient from Group A shows retinal thinning, smudge effect, loss of ellipsoid zone, and foveal deposits (b)

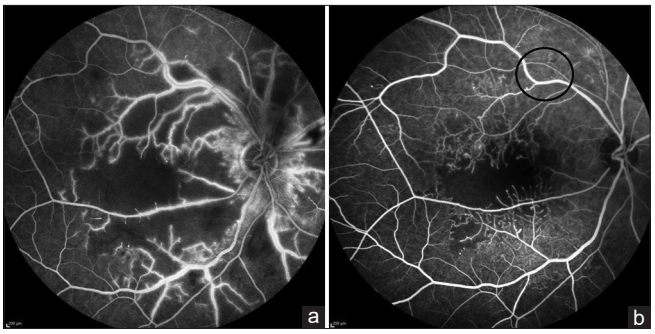

Figure 2: FA scan during the active stage of ER in a 48-year-old male from Group A showing occlusion of the second-order vessels, vasculitic leakage, and hypofluorescence at the site of the resolving retinitis lesions (a). FA image of the same eye 6 years after the resolution shows partial reperfusion of the occluded vasculature and persisting capillary non-perfusion (encircled) at the previous retinitis lesions (b)

Table 1: Demographic and clinical parameter comparison

	Group A	Group B	*P*
Eyes/Patients	25/20	25/23	
Sex (Male: Female)	16:4	11:12	0.029
Age	45.6 (range: 17-70, SD: 12, median: 45)	34 (range: 11-64, SD: 17, median: 27)	0.008
Diabetes mellitus	7 (35%)	1 (4.3%)	0.01
Skin rash	2 (10%)	10 (43.4%)	0.07
Joint pain	4 (20%)	10 (43.4%)	0.452
Latent period	20.6 (range: 7-90, median: 15) SD: 18	16.7 (range: 5-40, median: 14) SD: 10	0.392
Symptoms and eye check-up delay (days)	16.5 (range: 5-30, median: 15) SD: 9	8.4 (range: 3-15, median: 8.5) SD: 3	0.005
Presented to tertiary eye care (weeks)	9.6 (range: 1-32, median: 4.5) SD: 9	2.5 (range: 0.5-12, median: 1) SD: 3.3	0.001
Mean CDVA at presentation	20/400 (range: 20/125-20000) SD: 0.83	20/320 (range: 20/80-20000) SD: 0.69	0.017
Mean CDVA at resolution	20/400 (range: 20/200-20/20000) SD: 0.42	20/40 (range: 20/20-20/80) SD: 0.20	0.000
Bilateral presentation	18	14	0.029
KPs (non-granulomatous)	12	5	0.014
Fundus photo: number of retinitis lesions	4.3/11 (range: 1-11) (median: 4)	2.8/21 (range: 1-6) (Median: 3)	0.349
Disc pallor	14/23 (60.8%)	6/23 (26%)	0.017

Table 2: Imaging parameter comparison

	Group A	Group B	*P*
CMT	948.5 (range: 520-1553) SD: 261 (*n*=17)	912.2 (range: 615-1250) SD: 223 (*n*=25)	0.672
Retinitis ≤1500 µm of foveal center	16/17 (94.1%)	25/25 (100%)	0.22
EZ Loss	15/23 (65.2%)	8/18 (44.4%)	0.183
Retinal thinning	21/23 (91.3%)	10/18 (55.5%)	0.008
Foveal deposits	11/23 (47.8%)	2/18 (11.1%)	0.012
Smudge effect	13/23 (56.5%)	3/18 (16.6%)	0.009
FA vasculitic leakage	13/16 (81.2%)	4/6 (66.6%)	0.467
FA Neovascularization	4/16 (25%)	0/6 (0%)	0.176
FA occlusion of second-order vessels	5/16 (31.2%)	0/6 (0%)	0.119

Table 3: Investigations and treatment comparison

	Group A	Group B	*P*
Chikungunya	2 (IgM-1, IgG-1)/16 (12.5%)	0/18 (0%)	0.122
Dengue (IgG)	4/17 (23.5%)	3/19 (15.7%)	0.774
WIDAL	0/11 (0%)	3/14 (21.4%)	0.102
WFT	4/15 (26.6%)	11/21 (52.3%)	0.123
Doxy started within 2 weeks	6/19 (31.5%)	12/23 (52.1%)	0.179
Steroids without doxy cover	15/20 (75%)	10/20 (50%)	0.102
Anti-VEGF	11/25 (44%)	5/25 (20%)	0.069
PST/IVTA	6/25 (24%)	5/25 (20%)	0.733
Resolution of macular edema	36.46 (*n*=15) (range: 17-60) (Median: 40) SD: 14	33 (*n*=19) (range: 15-90) (Median 30) SD: 18	0.324
Resolution of retinitis	40.3 (*n*=15) (range: 20-70) (Median: 40) SD: 15	36.7 (*n*=17) (range: 14-120) (Median: 30) SD: 23	0.296

SD: Standard deviation, CDVA: Corrected distant visual acuity, KPs: keratic precipitates, CMT: Central macular thickness, EZ: Ellipsoid zone, FA: Fluorescein angiography, WFT: Weil-Felix Test, VEGF: Vascular endothelial growth factors, PST: Posterior subtenon's injection, IVTA: Intravitreal triamcinolone acetonide, Doxy: doxycycline

involvement. In contrast, only 31% of the cases received doxycycline within 2 weeks of ocular symptoms in Group A, but the difference was not statistically significant. Similarly, more cases in Group A received steroids without doxycycline cover compared to Group B but the difference was statistically insignificant [Table 3]. The number of eyes receiving periocular or intraocular steroids was comparable in both the groups but the number of eyes receiving intravitreal anti-vascular growth factor (VEGF) was significantly higher in Group A, although statistically insignificant. The duration of the resolution of macular edema and retinitis did not vary much between the groups [Table 3].

Discussion

In this study, we retrospectively analyzed factors affecting visual outcomes in ER, especially the factors other than presenting macular edema and location of retinitis lesions. We had first isolated cases which had a poor visual gain (CDVA 20/200 or worse) (13.6%) at the resolution (Group A). After studying the patients' clinical examination data and findings on OCT scan, it was noted that the patients with significant macular edema (mean CMT 948.5 μm) and retinitis lesions close to the center of the fovea (within 1500 μm) at the presentation had poor visual outcomes. To study other clinical, demographic, and treatment factors responsible for poor visual recovery, we formed Group B with comparable presenting severity, that is the macular edema and the location of retinitis similar to the eyes in Group A, but with better vision at the resolution (20/200 or better). We found that older age, male gender, diabetic status, delayed presentation, poor presenting CDVA, bilaterality, presence of keratic precipitates, disc pallor, retinal thinning, and subfoveal deposits had a statistically significant association, whereas the absence of skin rash, loss of ellipsoid zone, negative WIDAL, Weil-Felix test, and late doxycycline therapy or use of steroids without doxycycline had a statistically insignificant association with poor visual outcomes in ER.

None of the patients with diabetes had diabetic retinopathy in this cohort, but more diabetics ($n = 7$) were seen in Group A, five of which had uncontrolled blood sugar at the presentation. We believe the presence of uncontrolled diabetes could be an important systemic factor responsible for the poor visual outcomes in the ER. The use of systemic steroids in the treatment of ER may further worsen the diabetic status. Oral doxycycline without steroids has been reportedly shown good outcomes in the treatment of ER.[3] One may opt for the steroid-sparing therapy in ER, especially in patients with uncontrolled diabetic status. In this study, we had four patients who received oral doxycycline monotherapy in Group B whereas none in Group A. A local steroid depot injection is another option reported in the treatment of ER, as shown by Sreelatha *et al*.[8] in their series of 12 patients who had better visual outcomes with posterior subtenon's injection of triamcinolone acetonide. But among the 11 cases of ours who received periocular or intraocular steroids almost 50% had poor visual outcomes [Table 3].

The presence of skin rash and positive WFT or WIDAL could have been the decision-making factors for initiating antibiotic treatment in our study. Only three patients (Group A: 1, Group B: 2) in this cohort who had skin rash did not receive doxycycline and two of them were pregnant females (Group B). High prevalence of skin rash and positive WFT or WIDAL test in Group B could be the reason the patients in Group B received doxycycline therapy within 2 weeks of the disease, which perhaps could be important although not statistically significant factor responsible for better visual outcomes. Here, one must understand that the WFT has low sensitivity and specificity, and demonstration of a four-fold increase in titer is recommended to suspect rickettsial diseases.[9] Unfortunately, this was not possible in our patients as the test was not done at the onset of the fever in most of the cases by their physician. But it has been recently shown that the positivity or negativity of the WFT does not influence the visual and therapeutic outcomes when treated with oral doxycycline monotherapy.[10] Secondly, a mere positive WIDAL may not be diagnostic for typhoid. The cross-reactivity of WIDAL and WFT is well-known.[11] The diagnosis of rickettsial typhus fever can be confused with typhoid.[12,13] Thus, we deduce that commencing early doxycycline therapy despite a negative WFT in Group A would have prevented poor visual outcomes to some extent.

Most of the eyes ($n = 11$) which received intravitreal anti-VEGF injections were in Group A. Eight eyes in Group A and five eyes in Group B received anti-VEGF without doxycycline cover within 2 weeks of the onset of the disease. Thus, correlating anti-VEGF therapy with poor or better outcomes cannot be concluded from this study. Assessing the efficacy of anti-VEGF is beyond the scope of this study. Sunder *et al*.[2] found better results with anti-VEGFs in their study where their patients received anti-VEGFs along with doxycycline and steroids. But a comparative study, although with a small sample size did not find an additional benefit of anti-VEGFs in ER when treated with doxycycline and steroids or even with anti-VEGF monotherapy.[14] The use of anti-VEGF agents is tempting in the presence of macular edema and neovascularization without significant capillary non-perfusion areas in ER. But regression of neovascularization with mere oral doxycycline has also been reported.[15] Larger controlled studies are needed to evaluate the use of anti-VEGF agents on visual outcomes in ER.

Interestingly, no significant difference was found in the time taken for resolution of macular edema and retinitis lesions in both groups [Table 3]. Retinal thinning, foveal deposits, and optic disc pallor perhaps decided the final visual gain. The OCT parameters predicting visual outcomes in ER have been very recently reported by Biswal *et al*.[7] As in their study, we also found subfoveal deposits and optic disc pallor responsible for poor visual outcomes. In addition to those factors, they have also found the height of subretinal fluid at presentation as one of the contributory factors. In our study, CMT at the presentation was comparable in both the groups but the visual outcomes were different. In contrast to their study, we considered retinitis lesions within 1500 μm of the center of the fovea, which was comparable in both the groups but still the visual outcomes were different. As demonstrated in Group B despite high CMT and retinitis lesion within 1500 μm of the foveal center, the eyes had better visual outcomes. Biswal *et al*.'s[7] study found no statistically significant correlation between age, systemic illness, the interval between fever and retinitis, area of retinitis, different treatment modalities, and the final visual gain. This is in contrast with our findings that older age, diabetic status, and delayed ophthalmic checkups had a significant correlation with the final visual outcome. Unlike their report, we have also studied FA findings to compare in both groups. It is now known that the retinitis lesions after resolution leave behind capillary non-perfusion areas which are permanent.[16,17] A case from Group A in our study supported these findings, and in addition, demonstrated partial reperfusion of vasculature after 6 years [Fig. 2]. Almost all our cases had retinitis lesions at the fovea suggesting macular ischemia which was reflected as hypofluorescence areas on FA. In addition, we also studied the occlusion of the second-order vessels on FA images and discovered that 31.2% of the cases in Group A had occlusion of second-order vessels whereas none in Group B but again statistically insignificant.

Variable and uncertain etiology of ER may add the treatment bias while studying the final visual outcome. But a similar morphological pattern, a similar course of the disease, seasonal variation, and response to doxycycline and steroids allow us to study this uveitis as a single entity despite variable positive serological laboratory investigations.[1,13] The limitations of this study were that the groups were not age- and sex-matched. They were also not matched for the time of presentation and number and the area of retinitis lesions. The consideration of "retinitis lesions within 1500 μm of the center of fovea" in our study is a wider area when it comes to the assessment of the visual outcomes. Ideally, the involvement of the foveal center should have been studied. But those biases were permissible, as otherwise, they would have considerably decreased the numbers needed for a comparative study. Secondly, the progression of retinitis lesion toward the center of the fovea in Group A and non-progression of the lesion in Group B due to certain factors cannot be ruled out. Unfortunately, the documentation of such progression was not possible in our study as the imaging records before presentation were not available in most of our cases. The quality of the vision including visual fields as well as the SD-OCT-angiographic parameters was also not assessed in this study. Adding to this is the possible bias due to the inclusion of both eyes in seven subjects. In order to address this bias, we performed a statistical analysis where we excluded the eyes with better visual acuity from those seven subjects where both eyes were included. And the statistical analysis was performed for the effect of doxycycline started within 2 weeks, steroids without doxycycline cover, and the smudge effect on SD-OCT scan. The results we obtained were consistent with the original results. It is thus fair to assume that while the bias is possible, it does not affect our final conclusions.

Conclusion

To our knowledge, this is the first comparative study which analyzed the demographic, clinical, imaging, and treatment factors responsible for poor visual outcomes in ER. Apart from the factors like diabetic status, delayed presentation, poor presenting visual acuity, disc pallor, retinal thinning, subfoveal deposits, and EZ loss which can be logically implicated for poor treatment outcomes, our study has also found that although statistically insignificant, delayed doxycycline therapy and steroids without doxycycline cover can also be responsible for the poor visual outcome in ER. We also believe that this outcome may vary in different regions depending on the prevalence of the rickettsial diseases. Further studies using gold-standard investigation are needed to evaluate different treatment modalities and their correlation with the visual outcomes in ER.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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