Ocular Complications of Chikungunya Virus Infection during 2005-2006 epidemic

Running title: Ocular manifestation in Chikungunya fever

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UNDEARTAKING

Certified that the study “Ocular Complications of Chikungunya Virus Infection during 2005-2006 epidemic” is the original work undertaken by me at “Aravind Eye Hospital and postgraduate institute of ophthalmology”, SN High Road, Tirunelveli, Tamil Nadu- 627001.

I also certify that the work once accepted will hold the copyright for the Boolean Education (USAIM) and that the study will not be submitted to any other journal for publication.

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Abstract

**Purpose:** To present a case series of ocular complications following Chikungunya virus infection during a South Indian epidemic.

**Design:** Prospective, non-comparative, observational case series.

**Participants:** All patients with history of acute onset fever and joint pains (n=129) during the 2005-2006 epidemic of Chikungunya virus fever presenting at a tertiary eye care center in rural India between September and December 2006.

**Methods:** All patients underwent complete anterior and posterior segment examination. Neuro-ophthalmic evaluation and neuro-imaging was done for patients with cranial nerve manifestation. Serum was evaluated for Chikungunya specific immunoglobulin and investigations were done to rule out tuberculosis, typhoid fever, dengue fever and malaria. Relevant ocular findings associated with confirmed Chikungunya fever were recorded.

**Main Outcome Measures:** The characteristics, frequency, and locations of ocular lesions found in patient’s eyes were studied.

**Results:** Chikungunya infection was confirmed in 110 patients. Their mean age was 46.2±16.6 years and there was no age difference between males (n=60) and females (n=50). At presentation 59 (53.6%) patients were in recovery stage of systemic illness. Most common ocular complaints were redness (n=95, 86.4%), blurring of vision (65, 59.1%), pain (56, 50.1%) and watering from eyes (20, 18.2%). Bilateral ocular involvement was seen in 24 (21.8%) patients. Thirty-one patients (28.2%) had anterior uveitis characterized by pigmented keratitic
precipitates spread diffusely over the corneal endothelium. Twenty-six patients (23.6%) had visual pathway involvement; they were diagnosed as papillitis (n=13), retrobulbar neuritis (n=6), neuroretinitis (n=4) and inflammation of optic tract (n=3). Isolated or multiple involvement of third, fourth, sixth and seventh cranial nerve was also noticed in twelve patients. Herpes simplex like dendritic or geographic keratitis was seen in 19 (17.3%) patients and stromal keratitis was seen in five patients. Patients also presented with conjunctivitis, subconjunctival hemorrhage, scleritis, superior rectus myositis, vitreous hemorrhage, central serous chorioretinopathy, orbital apex syndrome, central retinal artery occlusion and ophthalmic artery occlusion.

**Conclusions:** Chikungunya infection forms an important differential diagnosis in inflammation of almost all ocular tissues and should be suspected in patients residing in or traveling through endemic or epidemic regions.
Main Manuscript

**Scope:** Chikungunya virus is an important arbovirus responsible for many epidemics of fever and crippling arthralgia throughout the world. It was first detected in a febrile human resident of Tanzania in 1953.\(^1\) Since then this virus is recognized as a cause for many epidemics along the tropical regions of Africa, South Asia and South America. In these areas the virus is maintained in endemic state through a sylvatic transmission cycle between wild primates and mosquitoes such as *Aedes luteocephalus*, *A. furcifer*, or *A. taylor*.\(^2\) Human to human spread of Chikungunya virus is mainly by *A. aegypti* and, to a lesser extent, by *A. albopictus* through an urban transmission cycle. In humans, it produces a febrile illness characterized by development of a stooped posture seen as a result of arthritic symptoms of the disease; hence its name Chikungunya which in Swahili means ‘that which bends’.\(^1\)

In 2005-2006, massive outbreaks of Chikungunya virus infection are reported from many islands in Indian Ocean, Southeast Asia and the Pacific region.\(^3\),\(^4\) The virus was also isolated among residents of non-endemic countries who travelled to the affected regions during the outbreak.\(^5\),\(^6\) In India alone, millions of peoples were affected by this disease. *Aedes Aegypti* is the main vector responsible for virus spread in India.\(^3\) During this epidemic increased occurrence of, premature deaths and severe systemic infections involving the central nervous system, visceral tissue, neonates were noticed.\(^7\) This change in disease characteristic is probably due to evolution of Chikungunya virus proteins responsible for this epidemic.\(^8\)

Severe ocular complications associated with Chikungunya infection are not classically reported so far. With this study, we report a series of patients with ophthalmic symptoms during the 2005-2006 epidemic of Chikungunya fever and describe the spectrum of manifestations of these emergent ocular complications.
**Material and Methods:** This prospective, non-randomized, non-comparative, observational case series describe patients with acute onset of ocular symptoms during or following episode of fever and joint pains, presenting to a tertiary eye care centre in rural South India between September and December 2006. After obtaining informed consent, all patients with above symptoms underwent serological testing to confirm the Chikungunya infection. Their serum were collected and investigated for Chikungunya-specific immunoglobulin M (IgM) antibody-capture enzyme-linked immunoabsorbent assay (MAC-ELISA) at the National Institute of Virology, Pune, India.

All enrolled patients underwent complete ophthalmic examination, including best-corrected Snellen visual acuity, tonometry, and slit-lamp biomicroscopy of anterior and posterior segments. In addition, slit-lamp photography, Hess charting, color vision testing with Ishihara charts, central visual field testing with tangent screen or Humphery visual field analyzer, fundus photography, optical coherence tomography, visually evoked potentials, computerized tomography or magnetic resonance imaging were performed on the basis of clinical diagnosis. Complete blood profiles, platelet counts, peripheral blood smear, tuberculin syringe test (Mantoux test), Venereal Disease Research laboratories test and Widal test were performed to exclude dengue fever, malaria, tuberculosis, syphilis and typhoid fever. Ocular findings of all patients were documented and data sheets were prepared using Microsoft excel 2004. All investigations were performed according to the guidelines of the Declaration of Helsinki. This study was conducted at site that has no Institutional review board/Ethics committee, but prior consent from the hospital advisory board and informed consent from the study participants were obtained.

Diagnosis of Chikungunya infection was confirmed if patient had acute onset fever with joint pains of varying severity, negative tests for malaria, typhoid, tuberculosis and dengue, and positive anti-Chikungunya antibodies (IgM) in serum. Clinical features of confirmed Chikungunya infected patients are presented in the results.
Observations and Outcomes:

**Demographics:** One hundred and twenty-nine patients presented for ocular examination had history of fever and joint pains. Of these 112 patients were positive for Chikungunya IgM on serological testing; 14 had negative Chikungunya serology whereas serum samples of three patients were damaged during transit. Three patients had positive test for tuberculosis and two patients were positive for dengue fever; two of these were also positive for Chikungunya IgM and were not included in analysis. Mean age of remaining 110 Chikungunya positive (confirmed patients) patients was 46.2±16.6 years (range, 10-82). There was no age difference between male (n=60, 54.5%) and female patients (n=50, 45.5%). All patients were of Indian origin.

**Symptoms:** Patients in addition to fever and joint pains also had headache (n=22, 20%), bodyache or malaise (18, 16.4%), vomiting (15, 13.6%), haematuria (2, 1.8%). Ocular symptoms developed 20.7±29.8 days (range, 0-120) after the onset of systemic illness. Fifty-nine patients (53.6%) were recovering from their systemic illness when they developed ocular complaints. Patients reported with eye redness (95, 86.4%), blurred vision (65, 59.1%), pain (56, 50.9%), watering (20, 18.2%), photophobia (15, 13.6%), diplopia (8, 7.3%), inability to close eye (5, 4.6%), irritation (3, 2.7%), and drooping of eyelid (2, 1.8%). Bilateral ocular symptoms were seen in 24 (21.8%) patients; 86 had unilateral ocular involvement.

**Clinical features:** Involvement of sclera, cornea, anterior uvea and cranial nerves supplying the eyes was seen in 95 patients (86.4%). Inflammatory cranial nerve disease (38, 34.6%), anterior uveitis (31, 28.2%) and herpes simplex virus like keratitis with or without infiltration (31, 28.2%) were the most common findings in our patients. Ocular signs were limited to single structure in 91 (82.7%) patients and involved more than one ocular tissue in the remaining 19 patients. A detail of clinical diagnosis in all patients is presented in table 1.
<table>
<thead>
<tr>
<th></th>
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<th>Bilateral involvement</th>
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<tr>
<td>Total number of cases</td>
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<td>86 (78.2%)</td>
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<td>22</td>
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<td>2 (22.2%)</td>
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<td>0 (0%)</td>
<td>2 (100%)</td>
<td>2</td>
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<td>Orbital apex syndrome</td>
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<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>CRAO</td>
<td>1</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td></td>
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<tr>
<td>Ophthalmic artery occlusion</td>
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<td>0 (0%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>Nystagmus</td>
<td>1</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>Negative results</td>
<td>-</td>
<td>4 (28.6%)</td>
<td>10 (71.4%)</td>
<td>14</td>
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<tr>
<td>Damaged sample while transit</td>
<td>-</td>
<td>0 (0%)</td>
<td>3 (100%)</td>
<td>3</td>
</tr>
</tbody>
</table>

CHIKV IgM= Chikungunya Immunoglobulin, HSV=Herpes Simplex Virus, IOP= Intraocular pressure, CRAO=central Retinal Artery Occlusion, CSR= Central Serous Retinopathy
Clinical features in patients with uveal tissue involvement: Thirty-one patients had anterior uveitis; they had characteristic mild to moderate sized pigmented keratitic precipitates spread diffusely over the back of cornea and mild to moderate anterior chamber reaction (Hogan et al grading). Of these, nine patients had transient rise in intraocular pressure, three eyes had associated stromal edema, two had Koeppes nodules on the pupillary border, four had pigment deposits on the anterior lens surface, and three had mild vitreous cells. One patient had associated nodular anterior scleritis, one had complicated cataract, one had sclero-keratitis and one had diffuse scleritis with complicated cataract. Patients with infective keratitis also had varying degree of anterior chamber reaction.

One patient, 10-year-old male, had panuveitis; he presented with pigmented keratitic precipitates, hypopyon, posterior synechiae, vitreous cells (grade 4+) and vitreous membranes in left eye. Fundus was faintly visible. His visual acuity at presentation was hand movements. Additional blood investigation for toxoplasmosis and leptospirosis were negative. He improved to 6/18 following core vitrectomy and on management with topical and systemic steroids. After one month he developed neuroretinitis; he presented with disc oedema, peripapillary flame shaped hemorrhages, and macular star exudation.

Clinical features in patients with corneal involvement: Nine patients presented with dendrite shape (two had bilateral involvement) and ten patients had geographical lesions similar to herpes simplex virus (HSV) keratitis. In eyes with dendritic keratitis, branching epithelial defects with terminal bulbs were seen spanning across the cornea (periphery to periphery); of them two patients had multiple lesions in same eye. In eyes with geographic lesions, the epithelial defects were large, involved nearly 1/3rd of corneal surface, located in paracentral/marginal cornea (nine eyes) and had superficial vascularization extending from the nearest limbus to edge of the defect. One eye had central corneal defect with no vascularization. Corneal sensation was absent in all the
above eyes. Three patients had past history of similar lesions suggesting recurrence of HSV keratitis in their eyes; rest all had primary ocular involvement.

Seven patients had infiltrative keratitis at presentation; five of them were diagnosed as bacterial keratitis, and two had fungal keratitis on microbiological evaluation (Grams stain and KOH smear). All patients developed ocular symptoms during resolution of their systemic illness. All of them were farmers, actively involved in their work during initiation of ocular problem. Two of them had seventh nerve palsy. None of them had eye trauma preceding the onset of eye complaints or had similar eye disease in the past. Corneal sensation was absent in these eyes.

Five patients had stromal keratitis (three had nummular lesions and two had disciform lesions), four had scleritis, and five presented with conjunctival involvement (Table 1).

**Clinical features in patients with cranial nerve/orbital involvement:** Inflammation of visual pathway (termed optic neuritis hereafter) was seen in 26 (23.6%) patients; six had bilateral involvement. All patients presented with sudden onset visual loss. Thirteen of them had papillitis, six had retrobulbar neuritis, four had neuroretinitis and three had inflammation of optic tract (termed retrochiasmal neuritis hereafter). Patients with papillitis had oedema of optic nerve head, peripapillary hemorrhages and exudates, and relative afferent pupillary defect. Patients with retrobulbar neuritis had relative afferent pupillary defect with normal retina and optic disc. Patients with neuroretinitis had oedema of optic disc and macula with hemorrhages and exudates at posterior pole arranged in an incomplete macular star pattern. Patients with optic tract lesion presented with incongruous homonymous field defects and normal pupillary reaction. Color vision defects, visual field defects and increased latency of visual evoked potentials were seen in all cases with papillitis, neuroretinitis and retrobulbar neuritis. Computer tomography scanning (CT-Scan) and magnetic resonance imaging (MRI) of brain were normal in all the above patients.
Seventh cranial nerve was the second most common nerve involved (five patients); of these three had exposure keratitis and one eye had associated papillitis. Isolated third and sixth nerve paresis was seen in two patients each. Isolated fourth nerve paresis was seen in two patients and fourth nerve paresis with optic neuritis was seen in one patient. CT-scan and MRI were normal in above patients.

Two patients had clinical feature suggestive of orbital apex syndrome (one had bilateral involvement). They presented with total external ophthalmoplegia and optic neuritis. Neuro-imaging was normal for these patients. One patient had unilateral restriction of elevation and abduction; MRI of this patient was suggestive of brain stem infarction. One patient had superior rectus myositis and presented with marked inflammation at the insertion of superior rectus with thickening of muscle belly noticed on CT-scan of orbit.

Other clinical features: Three patients presented with central serous retinopathy, two had vitreous hemorrhage, one had central retinal artery occlusion, and one had ophthalmic artery occlusion. One patient had nystagmus secondary to labyrinthine inflammation and presented with horizontal jerky nystagmus with fast component to left side.
Analysis and discussion: Chikungunya is a member of the Alphavirus genus of the family Togaviridae. Genus Alphavirus represents a group of enveloped viruses with single-stranded plus-sense RNA genome. Eastern Equine Encephalitis, Western Equine Encephalitis, Venezuelan Equine Encephalitis, River Ross viruses are other members of this genus. They are classified as arboviruses because they are maintained in nature through biological transmission cycle between susceptible vertebrate host and hematophagous arthropods, usually mosquitoes and ticks. Chikungunya virus infects human following bite of an infected A. Aegypti and to lesser extent A. albopictus mosquito.

In India, the Chikungunya outbreaks were recorded in 1963, 1964, 1965, and 1973. Phylogenic analysis suggested that Asian genotype of Chikungunya virus was responsible for these epidemics. Unlike other members of the genus alphavirus, Chikungunya virus was recognized to produce illness that was self-limiting and characterized by sudden onset of fever, headache, malaise, arthralgias or arthritis, myalgia, skin rash and low back pain and have incubation period of 2–4 days. Although Chikungunya fever typically lasts 3–7 days and full recovery was the usual outcome; certain patients experienced persistent joint symptoms for weeks or months and occasionally years after illness onset. Rare case of Chikungunya linked meningioencephelitis or neonatal infection were reported during 1973 epidemic.

During the 2005-2006 Indian epidemic, change in disease characteristic was noticed. Severe systemic infections which include central neurological disease, acute hepatic failure, multi-organ failure, neonatal infection (trans-placental or mosquito borne) and death were commonly noticed among infected individuals. This change in disease characteristic was probably due to evolution in viral structural and non-structural proteins of central/East-African serotype of Chikungunya virus responsible for this outbreak.

During the initial period of the Chikungunya fever epidemic, an increase in occurrence of anterior uveitis and optic neuritis was noticed. The negative tests for tuberculosis, syphilis, dengue, and typhoid fever and presence fever and joint
pains made us realize that this presentation was probably linked with emergence of Chikungunya virus in our region. Our investigation showed that majority of patients presenting with fever and joint pains during the epidemic were positive for Chikungunya antibodies (112, 86.8%). Of this 110 patients had confirmed Chikungunya infection. Confirmed Chikungunya infection was related with inflammation of almost all ocular tissues but cornea, uvea and the cranial nerves were most commonly affected.

In patients with Chikungunya related uveitis, the distribution of acute, pigmented, keratitis precipitates and pattern of anterior uveitis resembled with that of acute herpetic uveitis, but characteristically differed from white, discrete, well-spaced, and stellate-shaped keratitis precipitates seen in fuchs heterochromic uveitis. Similarly, dendritic or geographic keratitis in our patients resembled with those produced by herpes simplex type 1 or herpes zoster virus infection. It is possible that systemic illness might have triggered the reactivation of the herpes simplex virus in trigeminal ganglion. But absence of previous corneal or skin lesion in most of our patient’s suggested that reactivation may not be the cause of uveitis or keratitis in most of our patients. Also, according to Herpetic Eye Disease Study Group, systemic infection may not predispose to recurrence of ocular HSV disease. Presence of patients with ocular involvement during the initial illness of Chikungunya fever therefore raises speculations that ocular presentation was a possible result of direct invasion of eye structures by Chikungunya virus.

Presentation of one patient with panuveitis (hypopyon, posterior synechia and posterior segment inflammation) suggested leptospiral uveitis or Behcets disease as first differential diagnosis. Absence of mucosal lesions, absence of leptospiral antigens and response to steroid in absence of antibiotics helped in confirming the diagnosis in favour of Chikungunya infection.

Seven patients presented with corneal infiltration. Source of infection in these patients is unclear. These patients had spontaneous onset of ocular symptoms during the resolving stage of systemic illness. All patients belonged to rural area and were farmers by occupation. Three eyes had small infiltrate seen
within the geographic lesion similar to other patients. Four eyes had near total corneal infiltration with corneal thinning. It is possible that the corneal surface damage as seen with viral keratitis or surface exposure, and the nature of work would have predisposed the corneal surface to development of corneal infiltrate.\textsuperscript{18}

The pattern of cranial nerve involvement was variable in our patients. Visual pathway and optic nerve were commonly involved. Patients presented with papillitis, retrobulbar neuritis, neuroretinitis or inflammation of the optic tract. Rare occurrence of bilateral papillitis, neuroretinitis and retrobulbar neuritis was also noticed. Similar presentation can be seen with dengue virus, leptospirosis, syphilis, varicella zoster and mumps.\textsuperscript{16, 19-21} Similarly, virus infections can produce inflammation of third, fourth, sixth and seventh nerves leading to isolated or multiple cranial nerve paresis.

Tuberculosis, syphilis, leptospirosis, dengue, herpes simplex and herpes zoster are prevalent in our region and are important causes related with development of inflammatory eye disease.\textsuperscript{15, 16, 19, 22, 23} Viruses like mumps and West Nile can also have similar presentations.\textsuperscript{24, 25} In addition, Collagen vascular diseases like Wegner's granulomatosis, or HLA-related uveitis like Behcet's syndrome can produce inflammation of ocular and orbital structures.\textsuperscript{17, 26} HLA-B27 related acute anterior uveitis frequently associated with the seronegative arthopathies, such as ankylosing spondylitis and Reiter's syndrome are other common noninfectious conditions that mimic the clinical presentation of our patients with acute iridocyclitis.\textsuperscript{27} Clues in history, ocular and systemic examination, and investigative profile may assist in the diagnosis.\textsuperscript{28}

Systemic illness produced by dengue virus and malaria closely resembles with that produced by Chikungunya virus; this makes it mandatory to distinguish between these conditions.\textsuperscript{5, 19} Clinically dengue fever is associated with abrupt onset of fever with macular or maculopapular rash and blood dyscrasias (thrombocytopenia and neutropenia) and Dengue Shock Syndrome is associated with hypotension, narrowing of pulse pressure (<20 mm Hg), and circulatory failure. Absence of dermatological signs, thrombocytopenia and features of
Dengue Shock Syndrome in our patients helped us establish the diagnosis in favour of Chikungunya infection.

Chikungunya infection can be confirmed by Reverse-Transcriptase-Polymerase Chain Reaction (RT-PCR) analysis and/or virus isolation. They are rapid, confirmatory tests of choice if the illness is less than four days duration. All our patients presented beyond four days of onset of symptoms, where the diagnosis was possible only by detection of Chikungunya specific IgM in patient serum. In our series 112 patients were positive for Chikungunya specific IgM. Two patients with positive Chikungunya IgM also had blood profile and serological test positive for dengue; one of them had vitreous hemorrhage and the other had unilateral optic neuritis. Three patients had positive montoux reaction suggestive of tuberculosis; one had Phlyctenular conjunctivitis and two had anterior uveitis (all three of them were Chikungunya IgM negative).

Exact mechanism of ocular involvement following Chikungunya infection remains unknown. Simultaneous occurrence of systemic and ocular disease in 59 patients suggests direct viral involvement of ocular structures. Late involvement of ocular tissues in 51 patients suggests a delayed immune response (post-viral infection) responsible for ocular disease. Antigenic mimicry between the stimulating virus derived antigens and normal or altered host tissue proteins, immediate hypersensitivity reactions and stimulation of a pathogenic lymphocytic reaction may be responsible for this delayed immune response.

Treatment for Chikungunya typically involves treating the symptoms and includes bed-rest and the use of non-aspirin analgesics during the phase of illness where the symptoms are most severe. There is no vaccine that protects against Chikungunya virus. Using protective measures to prevent being bitten by an infected mosquito remains the only means to reduce the risk of exposure. In absence of specific antiviral regimen the treatment of ocular disease is also supportive and involves use of steroids in controlling inflammation especially those with uvea involvement.
**Conclusions:** We suggest that inflammatory ocular disease can occur in association with Chikungunya infection. It is mainly an acute onset reaction that can involve any ocular tissue. Chikungunya infection should form an important differential diagnosis in individuals with ocular inflammation especially in those residing in tropical regions and in travelers to epidemic areas.
Figure and legends:

**Figure 1**: Clinical photographs of common ocular presentations associated with Chikungunya virus infection.

**Fig 1A**) Cornea photograph of a case with dendritic keratitis: A 70-year old male presented with pain, redness and photophobia developing on second day of Chikungunya fever, ocular examination of left eye showed branching epithelial defect with terminal bulbs (fluorescin stain positive) spanning across the cornea (periphery to periphery).

**Fig 1B**) Cornea photograph of a case with geographic defect and secondary infiltration: A 57-year old male developed acute onset pain and redness during his systemic illness. He was treated with native medications (Human milk) for 10 days. On presentation he had large geographic shaped epithelial defect, involving 1/3rd of corneal surface, located in paracentral/ central cornea, with superficial vascularization extending from the nearest limbus to edge of the defect and with infiltration of the base involving the anterior 1/3rd of stroma. Corneal scraping revealed *Streptococci pneumonia* on microbiology.
**Fig 1C)** Anterior segment photograph of left eye of a case with anterior uveitis: A 64-year-old female presented with bilateral pain and photophobia of ten days duration developing one month after resolution of Chikungunya fever. Ocular examination revealed mild to moderate sized pigmented keratitic precipitates spread diffusely over the back of cornea and mild to moderate anterior chamber reaction (Hogan et al grading).

**Fig 1D)** Anterior segment photograph of a case with panuveitis: A 10-year-old boy presented with defective vision of one month duration developing during an episode of chikungunya fever. Examination revealed pigmented keratitic precipitates, hypopyon, posterior synechiae, vitreous cells (grade 4+), vitreous membranes and dull fundus glow in left eye. His visual acuity at presentation was hand movements.

**Fig 1E)** Fundus photograph of a case with Optic neuritis: A 28-year-old developed blurring of vision in left eye of four days duration, two week after resolution of chikungunya fever. Examination revealed left eye relative afferent pupillary defect, optic disc edema and hemorrhage, defective color vision and inferior altitudinal defect.

**Fig 1F)** Fundus photograph of a case with neuroretinitis: A 65-year-old male complaint of blurred vision in left eye of 2 weeks duration developing during the recovery of Chikungunya fever. Examination revealed left eye relative afferent pupillary defect, optic disc edema and hemorrhages, macular edema and exudates in a fan shape, defective color vision and sectoral visual fields defect involving the macula.
References: