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Review

Ophthalmologic aspects of chikungunya infection

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Summary Chikungunya fever, a viral disease epidemic in some parts of the world is newly introduced in the Americas. This is of considerable international concern, with a growing incidence owing to developing urbanization, tourism, and trade. Ocular manifestations of chikungunya fever are not frequent, but of great relevance. Common manifestations include conjunctivitis, optic neuritis, iridocyclitis, episcleritis, retinitis and uveitis. Diagnostic and monitoring investigations would include optical coherence tomography, fundus fluorescein and indocyanine green angiography, visual field analysis, and electrophysiologic tests. There

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have been no prospective, randomized therapeutic trials, and it is unclear if the disease is self-limiting or if treatment is actually beneficial. Prognosis varies, ranging from full resolution to permanent vision loss despite intervention.

1. Introduction

Chikungunya virus (CHIKV) is a mosquito-borne viral disease caused by an arbovirus from the Togaviridae family and transmitted by species belonging mainly to genus *Aedes* [1]. Until December 2013, was endemic in parts of Africa and Southeast Asia and on the Indian subcontinent, but now is also endemic in tropical areas of the Americas [2—4]. This would be inferred given the longtime of transmission occurrence in this region and circulation of two genotypes, one clearly enzootic (East Central South African, ECSA, in Brazil) [1—4].

During 2014—2016, more than 2.0 million cases of chikungunya were reported in the Americas [1,5]. Some countries in the region have presented high incidence rates (>200 cases/100,000 pop) [5] such as Dominican Republic, El Salvador, Venezuela [4], Puerto Rico and Colombia [3]. The typical clinical signs of the disease are acute fever, severe arthralgia, and skin rash [6,7]. Complications include myocarditis, hepatitis, and neurological and ocular disorders, including a variety of anterior and posterior segment manifestations [7—11]. In this review we have addressed major features of the ocular compromise in this emerging arboviral disease, including its implications for travel medicine practitioners.

2. Laboratory diagnosis of systemic illness

Based on guidelines published by the Pan American Health Organization/World Health Organization (PAHO/WHO), polymerase chain reaction (PCR), virus isolation, or detection of viral antigens should be used before the eighth day of illness. After 8 days, chikungunya serologic tests such as IgM ELISA/rapid tests or IgG paired sera should be used because the viral load will have decreased [12].

3. Classification of systemic illness

CHIKV can cause acute, sub-acute, and chronic disease. Acute disease is most often characterized by sudden onset of high fever (typically greater than 102 °F [39 °C]) and severe joint pain. Other signs and symptoms may include headache, diffuse back pain, myalgias, nausea, vomiting, polyarthritis, rash, and conjunctivitis (reported in 3—56% of the cases). The acute phase of CHIK lasts for 3—10 days [1,6,12].

Rarely, severe forms of the disease can occur with atypical manifestations. Fatalities related to CHIKV infection are thought to be uncommon. However, an increase in crude death rates was reported during the 2004—2008 epidemics in India and Mauritius [13—15]. Recently, in Venezuela and Colombia, fatalities have been also reported during the 2014—2015 epidemics, these have occurred in elderly or those with underlying diseases [16,17].

Chronic disease is defined by symptoms that persist for more than three months. The frequency of persons reporting persistent symptoms varies substantially by study and the time that had elapsed between symptom onset and follow-up. Studies from South Africa note that 12—18% of patients will have persistent symptoms at 18 months and up to 2—3 years later [1,12]. Recently, new information pooling studies have provided data regard the post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) [5]. New models have estimated that the prevalence pCHIK-CIR would be 47.57% (95%CI 45.08—50.13%), with a median time of 20.12 months in which 50% of patients will develop pCHIK-CIR [5]. A recent meta-analysis found that the pooled prevalence of pCHIK-CIR from 18 selected studies among 5702 patients was 40.22% (95%CI 31.11—49.34%) [18]. Nevertheless, beyond the high prevalence of chronic complications is of concern the longtime of persistence, which recently have been shown as high as six years [19].

Ocular manifestations are included among the acute and/or severe forms of disease, but also in the chronic form (with less frequency), clearly deserving more studies, in endemic areas, as well in patients coming or returning from areas with transmission.

4. Ophthalmologic manifestations

Ocular involvement in chikungunya infection includes multiple manifestations ranging from the compromise on anterior segment to the development of lesions in the posterior pole [8,9]. Ocular manifestations can be present at the time of systemic illness or after resolution of systemic disease [8,9]. During the initial phase of the disease, while the systemic symptoms are being established, the first ophthalmological manifestation includes photophobia, conjunctival injection and retroocular pain [10,11,20]. It is common that other symptoms usually appears like blurred vision, floaters, watering, irritation and diplopia after a latent period of a month to a year (during chronic phase) [21—23]. It is difficult to clarify the exact interval between the beginning of fever in the context of the systemic disease and the establishment of eye symptoms, however, awareness about ocular manifestations of chikungunya should be raised. Some retrospective observational case series have made description of these features [24]. For instance, conjunctival injection can appear 10—12 weeks after fever beginning in the cases where this symptom does not appear with the beginning of systemic disease, decrease in vision is demonstrated after 4 weeks, pain and floaters can be present after 12 weeks of the fever beginning [24]. Beyond that, there is a lack of studies following

patients for long periods in order to assess timing of eye complications and duration of persistence.

4.1. Pathogenesis of ocular manifestations

The exact mechanism of ocular involvement following chikungunya infection has been not yet studied in detail. It has been described that pathogenesis in the systemic disease depends on viremia which is correlated with disturbance in the body temperature [10,24,25]. At this point, an immunological response and hypersensitivity reaction is started by antibodies against viral antigens, causing the articular compromise in the systemic disease and possibly the beginning of the ocular lesions. This is associated to variations in the virus genome leading to a change in the virulence and pathogenicity of the virus. Although this has not been fully tested, and the available data is related to East African and Indian Ocean strains of the virus, this is the potential mechanism involved [10,24—26]. There are some studies that make a pathogenic approach defining some of the target cells implicated in the beginning of the ocular disease. In the cornea, epithelium and endothelium cells are the preferred target of the CHIKV, while in the scleral connective tissue, stroma of smooth muscles of ciliary bodies and in the stroma of the iris, the fibroblast is the ideal cell for the virus because its high rate of replication leading to a huge production of infectious viral particles [27,28]. This preference to infect and replicate in epithelial, endothelial, and fibroblastic lineages has been reported by other various groups [29—31]. Keratocytes in corneal and scleral stroma, as well as cells of the corneal endothelium, have been found to be target cells of CHIKV [22]. Studies of the eye showed that CHIKV also targets fibroblasts in scleral connective tissue, in stroma of smooth muscles of ciliary bodies, in stroma of the iris, and between muscle fibers of ocular muscle [22]. These data demonstrate that CHIKV infects fibroblasts of eye tissues and that active replication in eye tissues leads to production of infectious viral particles in corneoscleral rims of donors [22].

4.2. Related ophthalmologic syndromes

The ophthalmologic manifestations present during or after the systemic disease include non-granulomatous anterior uveitis which is the most common manifestation, optic neuritis, retinitis, panuveitis, choroiditis, conjunctivitis, episcleritis and scleritis, and epithelial keratitis with dendritic lesions [7]. Some case series have estimated the frequency of these manifestations (Table 1) [10].

Table 1 Frequency of ocular manifestation during chikungunya infection reported in a case series in India [10].

CHIKV-associated ocular manifestations	*n*	%
Non-granulomatous anterior uveitis	10	27.03
Panuveitis	5	13.51
Optic neuritis	4	10.81
Lagophthalmos and VI nerve palsy	3	8.11
Retrobulbar neuritis	3	8.11
Keratitis	3	8.11
Multifocal choroiditis with cystoid macular edema	2	5.41
Exudative retinal detachment	2	5.41
Retinitis with vitreitis	2	5.41
Granulomatous anterior uveitis	1	2.70
Bilateral neuroretinitis	1	2.7
Central retinal artery occlusion	1	2.7

From Ref. [10].

4.3. Anterior uveitis

The classical symptoms of anterior uveitis secondary to chikungunya infection are not significantly different to those due to other causes, particularly from other arboviruses such as dengue [32]. It includes pain, conjunctival injection, decreased vision, photophobia and hypopyon. The presence of keratitic precipitates on the surface of corneal endothelium and stromal edema can be visualized during an ophthalmological examination [33]. The main complication related with anterior uveitis is the presence of posterior synechia, but are uncommon. It is possible to develop high intraocular pressure in the context of an open corneoscleral angle [21]. It is clearly established that chikungunya anterior uveitis can imitate a herpetic uveitis [34]. However, we can differentiate both because in the first one the compromise is more bilateral [35], exists past history of fever with joint pain, have being in endemic areas [3,20,36], and there are positive serologic results [11,21,35].

4.4. Posterior uveitis

This variety of uveitis is less common than anterior uveitis, and can be present with decrease vision, scotoma central, peripheral field defects and color vision defect. Symptoms in the anterior segment like conjunctival injection, pain, hypopyon are less frequent [21]. It is relevant to interrogate about associated involvement of the optic nerve head and/or the retinal vessels, the possibility that the clinical features correspond to a choroiditis, retinitis or retinochoroiditis or it is part of a panuveitis [37]. When posterior uveitis manifests as retinochoroiditis, the visual prognosis is poor [33].

4.5. Optic neuritis

Optic neuritis is characterized by acute or sub-acute loss of vision, pain with ocular movements and color vision defects [38,39]. It can be present as an anterior optic neuritis or as a retrobulbar optic neuritis and can be differentiated each other by edema in the optic nerve head [40]. It is unknown the precise mechanism why optic nerve is affected by chikungunya infection, even so it is presumed that an immune dysregulation, super antigen induction, hypersensitivity reaction and molecular mimicry between stimulating virus-derived antigens and normal or altered host tissue proteins may be the cause of the optic nerve damage [25,38—40]. In addition, with an increasing number of cases being reported associated to neurological complications, and the presence of viral antigens detected in

cerebrospinal fluid of patients, neurotropism is another plausible explanation for the potential neuroinvasiveness and dissemination of the virus through neural tissue [41—43]. Delay in onset, partial recovery of disc changes, bilateral involvement in few patients and good response to corticosteroid therapy, are pointers of an autoimmune etiology in optic neuritis related to chikungunya [39].

4.6. Retinitis

Retinitis is one of the manifestations in the context of chikungunya infection [44—46]. It may be present between 2 and 4 weeks after febrile period of systemic disease. Patients consult with a history of sudden vision lost without pain. It is usually accompanied by mild vitritis and presents areas of retinal whitening in the posterior pole [47]. Fundoscopy allows visualizing focal and multifocal patches of retinitis (Figs. 1 and 2), macular edema, serous detachment at the macula and localized involvement of the retinal vessel [46]. Chikungunya retinitis can simulate herpetic and West Nile virus retinitis [48,49], therefore, it is important to assess systemic symptoms to differentiate the etiology of the manifestation. All these patients have a good visual outcome with almost total recovery in 10—12 weeks [11]. Although not all the retinitis in a patient with chikungunya would be attributed to it, this should be considered in the differential diagnosis, even more in patients with no history of other systemic diseases that can affect the retinal tissues (e.g. high blood pressure, diabetes and other infectious diseases). In patient with chikungunya, the presence of ocular involvement (especially in patient with ocular signs or symptoms) should be assessed and suspect chikungunya as the cause if present.

4.7. Corneal and scleral involvement

According to case reports, involvement of corneal surface can include bilateral punctate superficial keratitis, stromal immune ring formation with underlying keratic precipitates which can resolve after 2 weeks of topical corticoid therapy [7,10]. Episcleritis and other manifestation in anterior segment are less frequent, but a good prognosis is reported with a complete resolution of symptoms and preservation of vision [24].

Summarizing, at Fig. 3, an eye diagram shows different parts/chambers involved in chikungunya infection with the most commonly reported clinical manifestations.

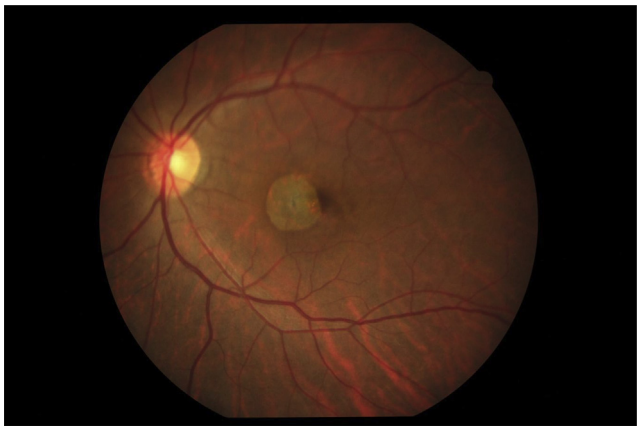

Fig. 1 Case of chikungunya infection with ocular manifestations: retinitis (38-years-old female patient from Chapainawabgonj, Bangladesh with severe arthralgia and myalgia for 1 month, visual acquity was 6/9, found positive for anti-Chikungunya IgM antibody). (Picture took by Fazle Rabbi Chowdhury).

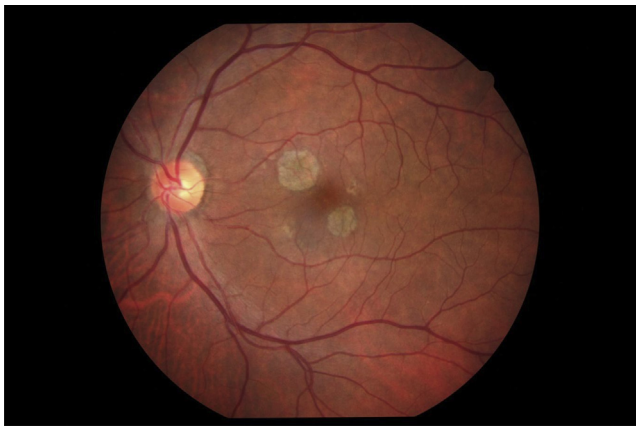

Fig. 2 Case of chikungunya infection with ocular manifestations: retinitis (30-years-old female patient from Sylhet, Bangladesh with severe arthralgia for 6 weeks, visual acquity was 6/12 on both eye, found positive for anti-Chikungunya IgM antibody). (Picture took by Fazle Rabbi Chowdhury).

5. Ocular diagnostic approach

Initial diagnostic approach of chikungunya ocular disease begins with the epidemiological suspicion based on the geographical origin and travel history of the patient to endemic areas (e.g. Latin American tropical countries, particularly Central America, the Caribbean, Colombia and Venezuela; Ocean Indic islands, India) [3,4,36]. Diagnosis of chikungunya systemic infection according to protocols established in global literature and ophthalmologic

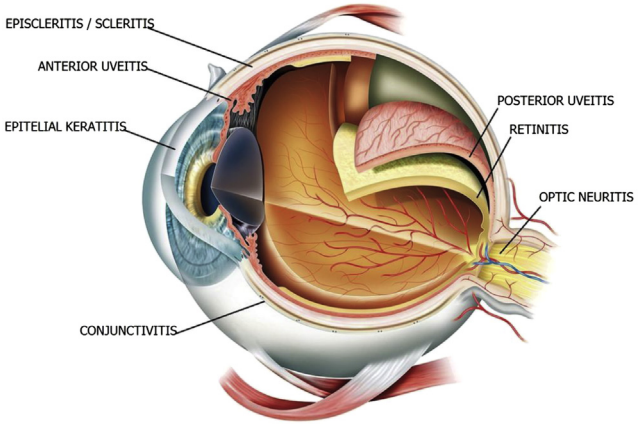

Fig. 3 Anatomic location of CHIKV-associated ocular manifestations.

symptomatology present in the patient are of utmost importance [12]. Cases of retinitis, fundus fluorescein angiography and optical coherence tomography may clarify the diagnosis with findings like early hypofluorescence with late hyperfluorescence, vascular leakage, and/or capillary non-perfusion in the fundus fluorescein angiography or areas of hyper-reflective with after shadowing in optical coherence tomography [11,50]. Other syndromic expressions of chikungunya ocular disease can be studied with usual ophthalmological equipment like slit lamp and funduscopy, considering the current lack of enough studies about the use of specific ophthalmological diagnostic methods for ocular manifestations of chikungunya virus [7,27,50—52]. Ocular investigations also include Amsler charting (a grid of horizontal and vertical lines used to monitor patients central visual field, useful in the detection of visual disturbances caused by changes in the retina, particularly the macula, e.g. macular degeneration, epiretinal membrane, as well as the optic nerve and the visual pathway to the brain), automated Humphrey visual field analysis (which is a test that can detect dysfunction in central and peripheral vision, caused by conditions such as glaucoma, stroke, brain tumors or other neurological deficits, also called perimetry when dedicated machinery is used), hyperflourescence at the fovea on fundus flourescein angiography, indocyanine green angiography, electrophysiological testing, and neuroimaging. Hyperflourescence at the fovea on fundus flourescein angiography, indocyanine green angiography and optical coherence tomography would be crucial in the assessment of the type and severity of ocular involvement because clinical signs may not be obvious, as has been reported in dengue [32].

In the case of infectious diseases and or primary care physicians, patient should be referred to the ophthalmologist in order to perform such specialized eye assessments.

6. Treatment considerations

In first place, although research in chikungunya has been benefited from 2005 to 2006 epidemics in La Reunion and in Italy during 2007 [53], there is not yet an approved antiviral therapy effective against the virus, neither an available vaccine [54—57]. Specific treatment for each chikungunya ocular manifestation does not differ from treatment for the same manifestation secondary to different etiologies. Anterior uveitis treatment consists of topical steroids and cycloplegic agents with optional use of topical beta blockers and oral or topical carbonic anhydrase inhibitors in increased intraocular pressure cases [11,22,24]. The resolution of symptoms was achieved in 1 week for anterior uveitis without ocular hypertension and within 4 weeks for those patients with increased ocular pressure, according to a case series in India [35]. Cases of posterior uveitis, panuveitis, keratouveitis and optic neuritis would benefit from the use of systemic steroids [7,24,39,44,45,58]. Early initiation with systemic steroid therapy like methylprednisolone or dexamethasone for 3 days followed by oral steroids could assist in the rapid recovery of visual function in patients with acute presentation of optic neuritis, but has no described role in the current literature when treatment is started at a late stage of the disease [38,39,59]. There are some reports about resolution of symptoms in retinitis after the use of steroids and systemic acyclovir, however there is no enough evidence about this conduct [21,24,45,47]. Beyond this, as happens with other systemic and non-systemic manifestations and complications, more research is urgently needed, particularly, as has been introduced, given the extensive epidemics in the Americas, ocular manifestations, even low in proportional frequency, would be seen in a considerable number of patients in this region as well in others where chikungunya is imposing a significant burden of disease.

7. Visual prognosis

It is clear that ocular prognosis is related to location of manifestation in the eye, like anterior segment or posterior pole, and the early initiation of an adequate treatment [24]. Anterior uveitis due to chikungunya infection has a good prognosis, better than in the posterior form, with total recovery if the steroid treatment is rapidly given [21,33,35]. According to a case series recently reported [39], about 90% of the patients with optic neuritis related to chikungunya infection with an early steroid treatment had improved visual function at day 3—10 after initiation of corticosteroid therapy, in terms of visual acuity, color vision, and visual fields, however when treatment was administered after 1 month of symptoms' beginning, there was not significantly visual improvement [39]. In a different case series it was established that 90% of patients with optic neuritis improved to visual acuity of 6/12 or better, 80% improved color vision and 60% had normal pupils without presence of relative afferent pupillary defect after steroid treatment [38]. Retinitis episodes had a favorable response to oral steroids irrespective of their prior systemic infection [46].

8. Conclusion

Chikungunya fever is increasingly seen in endemic and non-endemic regions as the result of increases in international travel, and thus ophthalmologists should have the requisite knowledge to diagnose and manage such patients, but also primary care and travel medicine clinicians should be aware that chikungunya can cause eye complications and then once suspected they should provide early referral to the eye specialist. In countries with endemic areas, now people are exposed to this and other arboviral diseases, that should be considered in the differential diagnosis. The main ocular complications of chikungunya fever are conjunctivitis, optic neuritis, iridocyclitis, episcleritis, retinitis and uveitis. Investigations were chosen based on the presentation of the disease and may involve hyperflourescence at the fovea on fundus flourescein angiography, indocyanine green angiography and optical coherence tomography. Thus far there have been no randomized control trials for treatment of chikungunya maculopathy. Other unresolved issues that may require further research are risk factors of chikungunya eye disease and also preventive measures for ocular complications. Prognosis is varied and ranged from full recovery to persistent visual loss and residual scotomata. Finally, more reports, including case-controlled

studies (as most are retrospective case series) [10,24,46,60] are necessary to assess whether eye findings are more common in persons infected with chikungunya, and even now, that Zika (also affecting the eye particularly in children) is circulating comparing between dengue, chikungunya and Zika [61—64].

9. Method of literature search

This review includes all published reports on ocular disease associated with chikungunya fever. English, Spanish and Portuguese language reports during the years 1950—2015 were reviewed. PubMed, Science Citation Index, Scopus, SciELO, LILACS and Google Scholar were the databases used for search. Key words (MeSH) used included chikungunya, eye, ocular, keratitis, iritis, choroiditis, uveitis, retinopathy, maculopathy, and optic neuritis. Historical reports identified through reference lists of these articles were also included, but did not encompass the main focus of this article.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Conflict of interest

No conflict of interest declared.

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