Ocular Symptoms and Signs of Chikungunya Fever in Puerto Rico

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Objective: To determine what ocular symptoms and signs are most common and if there are any associations with comorbid conditions in patients with Chikungunya fever.

Methods: A retrospective data review and analysis of the ocular symptomatology of 139 patients with Chikungunya fever who visited a local emergency room from August through September 2014. Frequencies were calculated, and Pearson's chi-square test employed. All the patients were confirmed as having Chikungunya with IgM (ELISA) before admittance into the study.

Results: Of the 139 patients, 42 (30.2%) had red eyes, 27 (19.4%) had conjunctivitis, and 13 (9.4%) had symptoms related to anterior uveitis, such as unilateral red eye, ciliary flush, or irregular pupil(s). Patients with a history of diabetes, hypertension, or cancer were more likely to have both red eyes (p = 0.033) and the symptomatology of anterior uveitis (p = 0.006), while patients with nausea or vomiting were more likely to have red eyes only (p = 0.001).

Conclusions and Relevance: Red eyes, conjunctivitis, and anterior uveitis occur frequently in patients with Chikungunya fever. Systemic diseases, such as diabetes, hypertension, and cancer, may increase the risk of such ocular manifestations. Routine ophthalmic evaluation is warranted in patients with these medical conditions. The relevance of this study lies in the fact that this disease remains an important public health issue, since such ocular sequelae as may be present can range from mild to severe, either as an acute or a delayed manifestation. [*P R Health Sci J 2018;37:83-87*]

Key words: Chikungunya fever, Ocular symptoms and signs, Mosquito

Previous studies (1–4) have reported that patients with the Chikungunya fever (CF) have a viral disease characterized by the acute onset of fever, a maculopapular rash, and severe polyarthralgia. It is caused by a single-stranded RNA virus, which is a member of the genus Alphavirus and the family Togaviridae (1, 2). The Chikungunya virus is transmitted by the bite of the Aedes aegypti and Aedes albopictus mosquitoes (2, 5). This viral exanthem is endemic to Africa, Asia, and the Indian Ocean and Pacific Ocean.

The term "Chikungunya" is derived from an African dialect and literally means "to walk bent over," which phrase describes the gait (caused by the accompanying severe arthralgia) of patients afflicted with the virus (4).

The viral infection follows a predictable temporal pattern: an incubation period of 2 to 6 days followed by an acute phase characterized by fever, skin rash, myalgia, and headaches lasting an approximate 7 to 10 days (3, 5). Lastly, the recovery phase may persist for weeks to months, and the polyarthralgia and polyarthritis may continue to afflict the patient for months (5, 6).

The first epidemic outbreak of Chikungunya was reported in Tanzania in 1952 (7, 8). The first case reported in the Western Hemisphere was seen on the Caribbean island of St. Martin in December 2013 (5, 9). Afterwards, a significant number of new infections followed in the Caribbean islands, underlining the importance of understanding the full scope of CF and its clinical manifestations.

Previous studies (3–5) have reported that patients with CF may present with a wide array of signs and symptoms, which include malaise, fever, skin rash, headache, myalgia, vomiting, lymphadenopathy, and incapacitating arthralgia. More severe complications, such as myocarditis, nephritis, fulminant hepatitis, and meningoencephalitis, have also been reported (10, 11). CF is a rare tropical disease with limited documentation regarding and research into both its pathophysiology and the range of its manifestations.

Ophthalmic manifestations in patients with CF have been described to affect all layers of the eye and cause vision-threatening events (10, 12, 13, 14). Conjunctivitis, keratitis, episcleritis, and anterior and posterior uveitis are some of the most common ocular manifestations of the virus (10, 12, 13).

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More severe and uncommon complications include panuveitis, optic neuritis, central retinal artery occlusion, multifocal choroiditis, and neuroretinitis; exudative retinal detachments have also been described (10, 13, 14, 15).

A complete ophthalmic examination is warranted if ocular involvement is suspected by the primary care physician. Advanced diagnostic modalities such as optical coherence tomography, fluorescein and indocyanine green angiography, and visual field and electrophysiologic tests could assist in the diagnosing of vision-threatening events (16).

We report the ocular symptomatology and signs of 139 Puerto Rican patients with serologically confirmed CF.

Patients and Methods

A non-concurrent, non-randomized, retrospective analysis of the electronic medical records of the patients who went (August through September 2014) to the emergency room of a local regional hospital and received a presumptive diagnosis of CF was conducted. Specifically, the term "Chikungunya fever" was searched for in the database of said hospital. During the emergency room visit, peripheral blood was extracted from the aforementioned patients for an IgM immunoassay to confirm the presumptive CF diagnosis in those patients. The patients received the appropriate care and evaluation by an emergency room physician. An ophthalmological examination by the emergency physician consisted of an external examination of the eyelids, conjunctiva, and cornea. Only 2 patients received posterior segment examinations by an ophthalmologist at the time of the data collection.

One hundred and thirty-nine patients were included in the study, and their charts were reviewed. The history and clinical diagnosis of each were assessed. The serological (IgM) diagnosis was performed at and confirmed by the CDC of Atlanta, GA, US. Descriptive statistical analysis was used for all the variables. Frequencies were calculated, and Pearson's chi-square employed. IRB permission was obtained from the IRB of the University of Puerto Rico Medical Sciences campus, with protocol B0430114.

Results

A total of 139 patients were included in the study. Of these, 79 (56.8%) were female and 60 (43.2%) were male. Eighty-six (61.9%) out of the 139 patients were aware of having had one or more mosquito bites 1 to 2 weeks prior to the onset of symptoms. Table 1 summarizes the sociodemographic data of the patients.

Symptomatology upon admission to the emergency room is summarized in Table 2. All patients presented with fever (100%). Myalgia, headaches, and polyarthralgia were the most frequent complaints in 119 (85.6%), 106 (76.3%), and102 (73.4%) cases, respectively. Existing arthritic symptoms were exacerbated in 34 (24.5%) out of the 139 patients. Nausea was reported by 43 (30.9%) out of the 139 patients. A cutaneous rash was described by 59 (42.4%) out of the 139 patients.

Table 1. Sociodemographic characteristics

		N	%
		139	
Gender			
Male		60	56.8
Female		79	43.2
Age, *y*, mean	36.4		
Distribution by age, *y*			
0–9		35	25.2
10–19		22	15.8
20–29		13	9.4
30–39		10	7.2
40–49		8	5.8
50–59		7	5.0
60–69		19	13.7
70–79		14	10.1
80–89		8	5.8
90–99		2	1.4
≥100		1	0.7

Table 2. Symptomatology

	n	%
	139	
Fever (>39°C)		
Positive	139	100.0
Negative	0	0.0
Polyarthralgia		
Positive	102	73.4
Negative	37	26.6
Headache		
Positive	106	76.3
Negative	33	23.7
Myalgia		
Positive	119	85.6
Negative	20	14.4
Arthritis exacerbation		
Positive	34	24.5
Negative	105	75.5
Nausea		
Positive	43	30.9
Negative	96	69.0
Vomiting		
Positive	22	15.8
Negative	117	84.2
Rash		
Positive	59	42.4
Negative	80	57.6
Myocarditis		
Positive	1	0.7
Negative	138	1533.3
Hepatitis		
Positive	0	0.0
Negative	139	100.0
Nephritis		
Positive	1	0.7
Negative	138	99.3
Bullous skin lesions		
Positive	0	0.0
Negative	139	100.0
Neurologic manifestations		
Positive	0	0.0
Negative	139	100.7

Myocarditis was reported in 1 (0.7%) patient during the recovery phase of Chikungunya infection. Moreover, 1 (0.7%) case of nephritis was reported as well. Hepatitis, bullous skin lesions, and neurological manisfestations were not present in any of the patients in this study (0%).

Red eyes were reported by 42 (30.2%) out of the 139 patients, and this included all red eyes (as described by the emergency physician) In which subconjunctival hemorrhage or dilation of the conjunctival and scleral vessels was observed. Watery and itchy eyes were reported by 27 (19.4%) out of the 139 patients. Conjunctivitis was described in 27 (19.4%) patients. Symptoms associated with anterior uveitis, such as unilateral red eye, ciliary flush, and irregular pupil, were reported by 13 (9.4%) patients. Symptoms associated with posterior segment involvement, such as floaters and decreased unilateral vision, were reported by 2 (1.4%) out of the 2 patients that received posterior segment evaluations. Table 3 summarizes the ocular symptoms reported by this patient population.

Table 3. Ocular symptomatology

	n	%
	139	
Red eyes: Subconjunctival hemorrhage and/or dilation of conjunctival and scleral vessels		
Positive	42	30.2
Negative	97	69.8
Conjunctivitis		
Positive	27	19.4
Negative	112	80.6
Unilateral red eye, ciliary flush, and irregular pupil		
Positive	13	9.4
Negative	126	90.6
Floaters and decreased unilateral vision		
Positive	2	1.4
Negative	137	98.6
Watery, itchy eyes		
Positive	27	19.4
Negative	112	80.6

Risk factors associated with ocular symptomatology in CF are summarized in Table 4. There were 38 (27.3%) patients who were 65 years of age or older. Hypertension, cardiovascular disease, and diabetes was reported in 35 (25.2%), 32 (23.0%), and 23 (16.5%) patients, respetively. Seven patients had a history of a malignancy; 15 patients showed some type of immunodeficiency, which was linked to his or her undergoing/having undergone chemotherapy or being HIV positive. Of the patients included, 86 recalled having been exposed to mosquitoes, only 1 patient had a history of recent travel outside of Puerto Rico.

All the patients had confirmation of CF by IgM radioimmunoaasay. Bed rest and increased fluid intake were recommended to all the patients. Of the 139 patients who visited the emergency room, 46 patients (33.1%) remained hospitalized and 93 patients (66.9%) were discharged home.

Table 4. Risk factors

	n	%
	139	
65 years or older		
Positive	38	27.3
Negative	101	72.7
Hypertension		
Positive	35	25.2
Negative	104	74.8
Diabetes		
Positive	23	16.5
Negative	116	83.5
Cardiovascular disease		
Positive	32	23.0
Negative	107	77.0
Cancer		
Positive	7	5.0
Negative	132	95.0
Immunodeficiency		
Positive	15	10.8
Negative	124	89.2
History of mosquito bites		
Positive	86	61.9
Negative	53	38.1
Travel history		
Positive	1	0.7
Negative	138	99.3

It was found that any ocular involvement was most likely to occur in patients that were 65 years old or older and who suffered from hypertension or diabetes or who had a history of cancer (X^2 = 3.952; p = 0.047). Moreover, a statistically significant relationship between developing Chikungunya virus–related anterior uveitis and having a positive past medical history of hypertension, diabetes mellitus, and/or cancer was also found (X^2 = 7.638; p = 0.011). In addition, patients who had a past medical history of hypertension, diabetes mellitus, and/or cancer significantly suffered more from red eyes due to CF (X^2 = 4.559; p = 0.033). Similarly, those with symptoms of nausea and/or vomiting were more likely to suffer from red eyes, as well (X^2 = 11.69; p = 0.001).

Discussion

CF is a rare disease that usually occurs in large outbreaks. The first reported epidemic outbreak of this disease occurred in Tanzania in 1952 (7, 8). Since then, outbreaks have been reported in Asia, Africa, and India (3, 5). It had long been considered a third-world infection, until recently, when outbreaks in Western Europe and the Caribbean were reported (3, 5). The increased incidence of cases in the Western world may be explained by the absence of herd immunity or by the development of a new strain of the virus (17, 18).

For this reason, not much is known about this illness; however, a high number of studies have been undertaken in recent years. Although some studies have reported the most common symptoms associated with the infection, not much has been published regarding the pathophysiology and sequelae of this tropical disease. Mahendradas and co-workers (13) and Weaver

and co-workers (3) reported that the most common symptoms of CF include maculopapular rash, polyarthralgia, myalgia, headaches, general malaise, and lymphopenia. In our series, the most common symptoms were myalgia, headaches, polyarthralgia, and rash. Our clinical systemic findings basically coincide with previous reports. Severe manifestations, such as encephalopathy, encephalitis, myocarditis, fulminant hepatitis, and multi-organ failure, have also been reported (3). Although not statistically significant, we found a case of myocarditis occurring several days after the acute phase of the infection, as well as a case of nephritis in a different patient during his acute phase. These findings are consistent with other cases reported in the literature (19, 20).

Both serological (IgM ELISA) and molecular (real-time PCR) methods can be used to diagnose CF (21). Molecular technique are widely accepted as being the most rapid for diagnosing CF; however, while these methods exhibit high sensitivity and specificity (21), they are limited by the short duration of viremia.21 Serological diagnoses seem to show sensitivity and/or specificity limitations, and different researchers have found inconsistencies with IgM (21). Therefore, the decision about which diagnostic method to use mostly relies on the stage of the disease. Molecular techniques, then, are preferable during the acute stage of CF, while serological methods are favored during and subsequent to the recovery period.

The ocular manifestations and consequences that this viral disease may have are less known and studied than the systemic manifestations are and have been. Mahendradas and co-workers (13), as well as Lalitha and co-workers (10), described the most common ocular findings in patients suffering from CF. These studies reported that anterior uveitis was the most common ocular manifestation of the Chikungunya virus infection, followed by posterior segment manifestations, which may present as retinitis, choroiditis, neuroretinitis, or optic neuritis (13). It is worth noting that ocular manifestations have also been reported as presenting weeks after a given individual's recovery from the acute phase of the illness, increasing the possibility that these manifestations are underreported (10, 13). Finally, a recent study reported finding bilateral ophthalmoplegia in a pediatric patient after CF (14).

In our study, subconjunctival hemorrhages in and/or dilation of the conjunctival and scleral vessels (described as red eyes) were the most common manifestation, followed by symptomatology suggestive of conjunctivitis, then by unilateral red eye, ciliary flush, irregular pupil(s), which might suggest the symptomatology of anterior uveitis, and, lastly, unilateral vision loss with floaters, which might also suggest posterior segment involvement. Our findings may differ from those reported by Mahendradas et al. A possible explanation for such a divergence is given by his team: Conjunctivitis may be underreported due to its (generally) benign course, the patient's prompt ocular recovery, and the time of evaluation (as conducted by Mahendradas et al) compared to that of our study, which evaluated patients who were in the acute phase of the disease only (12), accounting for the elevated prevalence that we noted.

Weaver and co-workers (3) described the severity of CF as depending on several variables, with age and the presence of systemic disease (e.g., diabetes, CVD) being two of them. The observed peak in incidence for children and young patients (Table 1) can be attributed to outdoor activities in which this population tends to participate; however, ocular symptomatology was more likely to be seen in elderly patients. We found that ocular involvement was most likely to occur in patients with systemic diseases. Any ocular involvement was more likely to occur in patients that were older than 65 years and suffered from hypertension (HTN) or diabetes or had a history of cancer. Similarly, patients who suffered from these systemic illnesses were more likely to develop Chikungunya-related symptoms of anterior uveitis than were those patients not suffering from any such illnesses. Chronic HTN and diabetes have lasting effects on the walls and endothelium of the ocular vasculature, resulting in increased exudation, hemorrhage, and disruption of the surrounding structures (22). We believe this may play a role in the increased risk of developing ophthalmological problems in patients with CF. The increased risk of infection in the immunocompromised or in patients that have undergone treatment for a previous malignancy may also have a role in the increased susceptibility to CF, a link that is similar to what has been found with other viral entities (e.g., cytomegalovirus) (22).

Regarding red eyes, patients were found to suffer from such more often if they also experienced nausea and/or vomiting or suffered from any of the previously mentioned systemic illnesses; a reasonable explanation for this would be the increased force, which ruptures the subconjunctival vessels. These findings are consistent with the principle stated by Weaver and co-workers (3), who observed that the course of Chikungunya tends to be more severe for those who suffer the comorbidities detailed above than it is for those who do not. Because of the results we observed, we recommend a complete prophylactic ophthalmic evaluation (during the acute and recovery phases of the fever) for any patient with the aforementioned risk factors; in fact, for patients with any visual complaints, further studies are warranted.

CF may be a clinical diagnosis, but many other viral diseases, such as dengue fever, may present in a similar fashion, making a definitive diagnosis desirable but challenging. The gold standard test for diagnosing CF is a viral culture (3, 5). Other methods for confirming a diagnosis of Chikungunya include RT-PCR (to amplify E2 fragments) and ELISA (to detect viral antibodies) (3, 5). All our patients were IgM positive.

The pathophysiology of CF is not completely understood, but it has been suggested to be a combination of a direct cytopathic effect (3, 10). Systemic CF treatment includes antipyretics and nonsteroidal anti-inflammatory drugs (13). Topical corticosteroids and cycloplegics are reasonable options to treat anterior uveitis caused by CF (13). Some healthcare providers have reported using acyclovir to treat posterior segment involvement of CF, although there is no evidence that this agent is effective against this virus (13). There is no standard, designated treatment for the ocular manifestations of CF. Nonetheless, systemic corticosteroids are used for patients with no contraindications for this therapy (10).

The limitations of this study include the low number of patients used to describe ocular findings. Another important limitation was the lack of proper ophthalmologic evaluation for concrete ocular diagnosis and ophthalmic follow-up at set intervals after recovery from the acute phase of the disease, making it impossible to detect additional ocular manifestations that may have presented after this phase. CF has been established as a geographically expanding disease. With over one third of our population remaining hospitalized, additional studies investigating the acute and subsequent phase along with the ocular findings in patients with CF are warranted. Studies regarding the severe manifestations of the infection—which include encephalitis, encephalopathy, myocarditis, fulminant hepatitis, and other multi-organ failures—given the prevalence/incidence and prognosis of same, are warranted, as well.

To our best knowledge, this is the first study in Puerto Rico to evaluate the clinical and ocular symptoms and signs of CF. The description of the emergency specialist is valuable as such specialists are the first physicians to encounter the patients afflicted with the virus. Further studies will elucidate the various types of uveitis seen in patients with the fever.

Resumen

Objetivo: Determinar qué manifestaciones oculares son más comunes en la fiebre de Chikungunya, y si existe alguna relación entre la sintomatología ocular y condiciones sistémicas en pacientes con la enfermedad. Métodos: Se llevo a cabo una revisión retrospectiva de datos de 139 pacientes con fiebre de Chikungunya, que visitaron una sala de emergencia entre agosto y septiembre de 2014. Se determinaron las frecuencias y se utilizó el análisis de Pearson Chi-cuadrado. El diagnóstico fue confirmado con IgM (ELISA, por sus siglas en inglés). Resultados: Ojos rojos se observaron en 42 (30.2%), conjuntivitis en 27 (19.4%); y síntomas relacionados a uveítis anterior como: ojo rojo unilateral, "flush" ciliar y pupila irregular en 13 (9.4%). Diabetes, hipertensión o cáncer aumentaron el riesgo a tener ojos rojos (p = 0.033) y a la sintomatología relacionada a uveítis anterior (p = 0.006). Los pacientes con náuseas o vómitos fueron más propensos a tener los ojos rojos (p = 0.001). Conclusiones y Relevancia: Ojos rojos, conjuntivitis y síntomas asociados a uveítis anterior se producen con frecuencia en pacientes con fiebre de Chikungunya. Diabetes, hipertensión y el cáncer pueden aumentar el riesgo de manifestaciones oculares en pacientes con la enfermedad. Evaluación oftalmológica de rutina se justifica en pacientes con estas condiciones médicas. Esta enfermedad sigue siendo un problema de salud pública, ya que las secuelas oculares pueden variar de leve a grave.

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