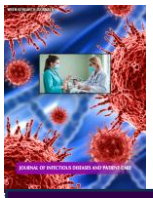

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Case Report

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Clinical Characterization of Oropouche Fever in Cuban adult Patients, 2024

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Abstract

Introduction: On May 27, the Cuban Ministry of Public Health reported an outbreak of Oropouche Fever (OF). This disease is caused by the Oropouche Virus (OROV), a member of the genus *Orthobunya*virus of the family *Peribunyaviridae*.

Objectives: To characterize the clinic and main laboratory findings of 47 OF confirmed patients treated at the Pedro Kouri Institute (IPK).

Methods: Case series study of patients treated at the confirmed to have Oropouche Fever by PCR-RT. All patients were following up for 30 days.

Results: 47 cases were studied, 27 women (60%), 60% white skin and the average age of 47 years being the most affected the age group of 41-50 years. Fever (95.6%), headache (91.1%), asthenia (88.9%), arthralgia (84.4%), myalgia (75.6%), low back pain (73. 3%), anorexia (68.9%), retro-ocular pain (57.8%), nausea (55.6%), chills and sweating (51.1%), diarrhea and fatigue (44.4%), vertigo (37.8%), abdominal pain (33.3%), photophobia (28.9%) were the most frequent symptoms. Symptom relapses occurred in 37.8% of patients at mean day 16 (SD 4.76) after onset of symptoms. Leukopenia was found in 26 patients (47.27%). The platelet count was below 150 × 109/L in 14 (25.45%) at 7 days after the onset of symptoms and in 2 (4.44%) cases at 30 days. Serum transaminase levels above 40 U/L behaved as follows. ASAT 10 (22.22%) at 7 days and 16 (35.56%) at 30 days. ALAT 8 (53.33%) at 7 days and 13 (46.43%) at 30 days.

Conclusions: The duration of the disease is not well defined and relapses are frequent; some symptoms and signs are similar to Dengue but with characteristics that allow differences to be established. There were no serious cases, GBS or deaths in the series studied at the IPK.

Keywords: Oropouche; Dysautonymia; Arbovirus; Disease; Fever; Headache; Asthenia; Arthralgia; Myalgia; Low back pain; Anorexia; Retro-ocular pain; Nausea; Diarrhea; Fatigue; Vertigo; Abdominal pain; Photophobia

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Introduction

Oropouche Fever (OF) is an arboviral disease caused by the Oropouche Virus (OROV), a member of the genus *Orthobunya* virus of the family *Peribunyaviridae*. This virus was detected for the first time in 1955 in the blood of a febrile forest worker, in the Vega de Oropouche village in Trinidad and Tobago. Approximately five years later, the circulation of the virus in epidemic form was detected in Belem, Brazil, with an estimated of 11,000 cases.

Subsequently OROV was identified in large epidemics or sporadic disease in tropical areas of Brazil and other countries in South and Central America [1-3]. On May 9, 2024, the Pan American Health Organization/World Health Organization (PAHO/WHO) issued an epidemiological alert on rising OF in South America with 5,193 cases in Bolivia, Brazil, Colombia and Peru as well as some autochthonous cases in non-endemic areas of Brazil and Bolivia [4]. The recent spread of the virus into nonendemic areas, the identification of vertical transmission and the first report of fatal cases have raised concerns about the threat that OROV poses at regional and global levels [5]. Although overall 500 000 cases of OF have been recorded in the American region since the first description, there is very limited knowledge of the disease. Most cases are mild, with symptoms similar to dengue, including headache, muscle pain, nausea and rash, with some cases of meningitis and encephalitis.

On May 27, 2024, the Cuban Ministry of Public Health notified the first OF outbreak in the country with the first confirmed cases in Santiago de Cuba and Cienfuegos provinces. Viral diagnosis was made at the Arbovirus National Reference Laboratory (Arbovirus NRL) of the Pedro Kourí Tropical Medicine Institute (IPK) [6-7]. In July, transmission had been confirmed in provinces of the center, east and west of the country with clinically suspected and confirmed OF cases. Taking into account that the Cuban outbreak represents the extension of the virus circulation to new geographic areas and that the circulating virus is similar to those reported associated with an increase in transmission in several areas of Brazil, we consider important describing the clinical picture of the disease in a group of adult's patients attended at IPK [8]. Patients were clinically followed up for30 days for possible sequels.

Methodology

The study includes 47 patients attended at IPK hospital with a suspected clinical picture of OF. Patients were questioned and clinically followed for 30 days after the first hospital visit. OROV infection was confirmed by RT-PCR in serum collected in the first 7 days of illness. RT-PCR for dengue, zika and chikungunya were negative. The cases were confirmed by RT-PCR with a mean of 6.4 days de que?

Patients included in the study were clinically evaluated at hospital visit and every 48 hours for the first 7 days after symptom onset and at 14, 21 and 30 days later. At each visit, a history, physical examination and laboratory tests (complete blood count, AST, ALT, blood glucose, creatinine and RT-PCR) were performed. Patients who were hospitalized received the same follow-up protocol. The reappearance of initial symptoms after an apparent clinical improvement after 10 days of symptoms onset was considered a disease relapse that may occur on more than one occasion, ruling out other diagnostic possibilities that explain the current condition.

Clinical and epidemiological data were collected in a database.

Ethical considerations

The study was approved by the IPK ethics committee. The ethical principles and values of human protection were considered during the whole study. Informed consent signature was obtained.

Results

47 OF confirmed cases were studied, of them, 27 (60%) %were women. According to the color of the skin, 60% were Whites, 26, 7%black and 13.3% mulattoes. The mean age was 47 years (SD 17.38) and the most affected age group was 41-50 years. The minimum age was 21 years and the maximum 86 years. Most of the patients (45) reside in Havana city (27 in La Lisa, 6 in Playa, 3 in Habana del Este and 2 in Arroyo Naranjo municipalities) Three patients visited the provinces of Artemisa, Mayabeque and Cienfuegos in the last 30 days previous to symptom's onset. Nine patients (19.4%) required hospitalization. 16 patients suffered arterial hypertension, 3 diabetes mellitus, 7 bronchial asthma, 2 obesity, 4 were smokers and one alcoholic. In 27 patients (57.4%) motive of hospital consultation was fever while 20 (42.5%) reported diarrhea, vomiting and abdominal pain. **Table 1** shows the most frequent signs and symptoms in the studied patients. Fever (95.6%), headache (91.1%), asthenia (88.9%), arthralgia (84.4%), myalgia (75.6%), low back pain (73.3%), anorexia (68.9%), retroocular pain (57.8%), nausea (55.6%), chills and sweating (51.1%) were the most frequent observed clinical manifestations. Less frequently, but very characteristic symptoms were diarrhea and fatigue (44.4%), vertigo (37.8%), abdominal pain (33.3%) and photophobia (28.9%).

Table 1: Comparison of the clinical signs and symptoms observed in Cuban and Brazilian patients *[8-10].

	Cuban patients, IPK, 2024	Parauapebas and Porto de Moz outbreak, Brazil (2003-2004)	MagalhãesBarata and Maracaná outbreaks, Brazil (2006)	Manaus outbreak, Brazil (2007)
Symptoms	No. (%)	%	%	%
Fever	43 (95.6%)	100	100	100
Headache	41 (91.1%)	79.3	99.3	72.7
Asthenia	40 (88.9%)	-	-	-
Arthralgias	38 (84.4%)	68.7	-	57.8
Myalgias	34 (75.6%)	30	46.9	70.3
Low back pain	33(73.3%)	-	-	-
Anorexia	31(68.9%)	-	-	-

Retrocular pain	26(57.8%)	-	-	-
Nausea	25(55.6%)	-	-	-
Chills	23(51.1%)	-	59.3	-
Sweating	23(51.1%)	-	-	-
Diarrhea	20(44.4%)	-	-	-
Fatigue	20(44.4%)	-	-	-
Rash	19(42.2%)	-	-	42.2
Vertigo	17(37.8%)	-	-	-
Relapse	17(37.8%)	-	-	-
Abdominal pain	15(33.3%)	-	-	-
Photophobia	13(28.9%)	-	38.1	-
Pruritus	10(22.2%)	-	-	-
Vomiting	8(17.8%)	-	-	-
Dysgeusia	8(17.8%)	-	-	-
Conjunctival injection	5(11.1%)	-	-	-
Lymphadenopathy	4(8.9%)	-	-	-
Ataxia	1(2.2%)	-	-	-
Hemorrhagic manifestations	-	-	-	15.5
Dizziness	-	-	39.8	-
Nausea/vomiting	8(17.8)	-	36.3	-

Fever is often high, up to 40 degrees Celsius and parieto-occipital headaches. Digestive symptoms can be the initial clinical manifestations, behaving like a gastrointestinal illness, characterized by vomiting, diarrhea, abdominal pain and dehydration. Other very characteristic symptoms are profuse sweating, fainting and intense pain at the lumbar spine. In 37.8% of patients, symptom relapse occurred an average of 16 days (SD 4.76) after illness onset. In these patients, the main signs and symptoms were fever, headache and dysautonomic symptoms such as profuse sweating, fainting due to orthostatic hypotension, dizziness and dry mucous membranes.

In 9 patients, symptoms relapsed three times. Relapse is characterized by the reappearance of symptoms after an initial improvement, which occurs in the second and third weeks after illness onset and can occur more than once. Relapses are characterized by the reappearance of fever, headache and dysautonomic symptoms, such as profuse sweating, fainting due to orthostatic hypotension, dizziness and dry mucous membranes, the most common. **Table 2** shows the results of the hemogram and blood chemistry. Leukopenia was observed in 26 patients (47.27%), platelet count (below 150 × 109/L) in 14 (25.45%) patients at day 7 of symptoms onset and in 2 (4.44%) at day 30. Serum transaminase levels above 40 U/L behaved as follows: ASAT 10 (22.22%) at 7 days and 16 (35.56%) at 30 days. ALAT 8 (53.33%) at 7 days and 13 (46.43%) at 30 days.

Table 2: Clinical laboratory findings in the studied Cuban patients, IPK, 2024.

Laboratory tests		Up to 7 days	Up to 30 days
Hemoglobin	Media (DE)	128,11 (19,43)	130,55 (17,80)
Hematocrito	Media (DE)	40 (6,01)	40,13 (5,05)
Leukocytes; n (%)	Media (DE)	4,8 (2,6)	5,63 (2,08)
Count platelets	<150 × 109 /L	14 (25,45%)	2 (4,44%)
	>350 × 109 /L	1 (1,82%)	5 (11,11%)
	Media (DE)	190,98 (63,93)	254,71 (74,58)
ASAT	>40 U/L	10 (22,22%)	16 (35,56%)
	Media (DE)	46,09 (15,83)	55,49 (44,55)
ALAT	>40 U/L	8 (53,33%)	13 (46,43%)
	Media (DE)	44,70 (18,60)	43,64 (25,44)
GGT	>40 U/L	6 (50%)	11 (42,31%)
	Media (DE)	44,16 (36,21)	34,19 (17,4)

Patient management

Most of cases (36) were managed on an outpatient basis but 9 required hospitalization. The main causes of hospitalization were intense dizziness with difficulty walking, as well as vomiting and diarrhea with dehydration. All cases were managed with symptomatic treatment, analgesics and hydration and were discharged 3-7 days after admission.

Discussion

OROV infection is characterized as an acute febrile illness, usually accompanied by headache, myalgia,

arthralgia, anorexia, dizziness, chills and photophobia. Some patients present a rash that resembles rubella as well as nausea, vomiting, diarrhea, conjunctive congestion, epigastric pain and retro–orbital pain. Other systemic manifestations have also been described. Meningitis associated to OROV infection has been reported.

Similar to the clinical manifestations reported during three large OF outbreaks in Brazil **(table 1)**, fever, headache, arthralgia and myalgia were frequently observed in our case series [9,10]. Additionally, asthenia, low back pain, anorexia, retroocular pain, nausea was also observed in more than 50%. Of interest was the identification in our patients of autonomic dysfunction symptoms such as profuse sweating (51.1%), diarrhea and fatigue (44.4%), vertigo (37.8%), abdominal pain (33.3%) and photophobia (28.9%). The involvement of the autonomic nervous system has been reported in other viral diseases, generally with a subacute or chronic course, but not in an acute and epidemic manner as we have observed in our OF cases. Autonomic dysfunction has been reported in retrovirus infections (Human Immunodeficiency Virus (HIV), human Tlymphotropic virus), herpesvirus, flavivirus, enterovirus 71 and lyssavirus [13].

More recently, autonomic dysfunction has been associated with SARS-CoV-2 infection. Direct tissue damage, immune dysregulation, hormonal alterations, elevated cytokine levels and persistent low-grade infection have been proposed as pathophysiological mechanisms. We do not know the implications of autonomic dysfunction during the OROV infection.

OROV infection has been associated with neurological complications and viral genomic RNA has been detected in the Cerebrospinal Fluid (CSF) of patients, suggesting its neuroinvasive potential. OROV is capable of infecting mature human neuronal cells in a context of preserved neuronal connections and brain cytoarchitecture [15].

Cases of OROV infection are generally self-limited and usually recover within a week, but there is the possibility of serious complications such as meningitis and encephalitis [16]. Early in the Cuban outbreak, Guillain-Barré Syndrome (GBS) was reported in three confirmed OF cases with virus RNA detection in the CSF of the three patients [17]. Progressively with the advance of the epidemic, the number of GBS cases increased. Additionally, patients with meningitis and encephalitis by OROV infection were reported [17]. These observations support that OROV is a causal agent of neurological disorders such as the autonomic syndrome, meningitis, encephalitis and GBS [17]. There was also a report in Brazil of acute Oropouche virus infections in 2 previously healthy women from a region outside the Amazon basin. The infections progressed rapidly to hemorrhagic manifestations and fatal outcomes in 4-5 days, so greater surveillance of the disease is needed [18].

In previous OF outbreaks, a recurrence of symptoms after recovery has been observed in approximately 60% of cases. Additionally, although most recover within a week, some patients have a prolonged convalescence. Serious complications, such as aseptic meningitis, are rare, but can appear in the second week of the disease; however, in our series a recurrence of symptoms was observed in 37.8% of cases during the 30 days after the onset of the symptoms [3]. Related to laboratory findings, only mild leukopenia is present, which does not fall below 2.0/L × 109/L. The platelet count showed a decrease below 150/L × 109/L in 14 cases (25.45%). These alterations do not have the periodicity of dengue, in which there is a progressive decrease from the third day of the onset of symptoms until the sixth or seventh day to show recovery [11]. Hemoglobin is maintained and the hematocrit does not show a progressive increase as in dengue infection. On the other hand, the affectation of liver enzymes occurs in approximately half of the cases, which did not show figures higher than 120 U/I.

Although most patients recovered within a week, some patients experience prolonged convalescence [3]. Approximately 60% of cases experience symptom relapses weeks after recovery; however, in our series, this only occurred in 37.8% of cases within 30 days of symptom onset.

Some of the limitations of our study are that analyzed data correspond to a group of patients treated at the institution based on the search for febrile cases according to the case definition proposed for surveillance. This means that patients who did not present fever would not be considered OF suspected cases. The lack of serological testing also means that cases can only be confirmed by RT-PCR in samples collected during the viremic phase. Finally, the data were collected in dengue-specific records with some modifications. Many suspected cases could not be confirmed because they attended consultations after the first week of symptoms onset during relapses and tested negative.

Conclusions

The duration of the disease is not well defined and relapses are frequent; some symptoms and signs are similar to Dengue but with characteristics that allow a differential diagnosis to be established. In our series, there were no serious cases, GBS or deaths.

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