ORIGINAL

Clinical, epidemiological and hematological characterization of hospitalized patients with clinical suspicion of dengue

Caracterización clínico epidemiológica y hematológica de pacientes hospitalizados con sospecha clínica de dengue

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ABSTRACT

Introduction: Dengue is one of the main viral epidemic diseases. The study of the clinical, epidemiological and hematological characteristics is essential for the prevention and management of cases. **Objective:** To characterize hospitalized patients with clinical suspicion of dengue from a clinical, epidemiological and hematological point of view. **Methods:** A descriptive, cross-sectional study was carried out at the "Amalia Simoni" Provincial Hospital of Camagüey, Cuba, during 2022. The sample was made up of 157 hospitalized patients with clinical suspicion of dengue. The variables analyzed were: age group, sex, month of diagnosis, signs and symptoms, hematological variables, leukocyte differential and days of onset of symptoms. **Results**: There was superiority in the 40-49 year age group (28.7%) and in the male gender (50.3%). In the month of August, 33 patients (21.0%) were reported and their main signs and symptoms were fever (90.4%) and headache (59.9%). In terms of hematological variables, hematocrit ranged between 0.42 and 0.48 and the platelet count ranged between 224 and 256 x 10^9/L. In the differential, the average number of polymorphonuclear cells varied between 0.62 and 0.72, and lymphocytes between 0.28 and 0.36. **Conclusions:** The sample studied was characterized by the preponderance of patients in the fourth decade of life who presented hyperthermia as a fundamental clinical manifestation. The study of hematological variables was essential in guiding the management of these patients.

Keywords: dengue; virus; prevention; platelets; hematocrit

RESUMEN

Introducción: El dengue es una de las principales enfermedades virales de naturaleza epidémica. El estudio de las características clínicas, epidemiológicas y hematológicas es fundamental para la prevención, tratamiento y evolución de los casos. **Objetivo:** Caracterizar desde el punto de vista clínico epidemiológico y hematológico a pacientes hospitalizados con sospecha clínica de dengue. **Métodos:** Se realizó un estudio descriptivo, de corte transversal, en el Hospital Provincial Clínico Quirúrgico Docente "Amalia Simoni" de Camagüey, durante el año 2022. La muestra quedó conformada por 157 pacientes hospitalizados con sospecha clínica de dengue. Las variables analizadas fueron: grupo de edad, sexo, mes del diagnóstico, signos y síntomas, variables hematológicas, fórmula diferencial de leucocitos y días de inicio de los síntomas. **Resultados**: Existió superioridad del grupo de edad de 40-49 años (28,7 %) y del sexo masculino (50,3 %). En el mes de agosto se reportaron 33 pacientes (21,0 %), mientras los principales signos y síntomas fueron la fiebre (90,4 %) y la cefalea (59,9 %). En cuanto a las variables hematológicas, la media del hematocrito osciló entre 0,42 y 0,48 y el conteo de plaquetas entre 224 y 256 x 10^9/L. En relación con la fórmula diferencial, el promedio de polimorfonucleares varió entre 0,62 y 0,72 y el de linfocitos entre 0,28 y 0,36. **Conclusiones:** La muestra estudiada se caracterizó por la preponderancia de pacientes en la cuarta década de vida, que presentaron hipertermia como manifestación clínica fundamental. El estudio de las variables hematológicas resultó indispensable para la evolución de los casos.

Palabras clave: dengue; virus; prevención; plaquetas; hematocrito

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INTRODUCTION

Dengue is a viral infection transmitted by mosquitoes. It is highly prevalent in tropical and subtropical regions, and is responsible for putting more than four billion individuals at risk globally. It is estimated that about 500,000 people with the severe form of dengue require hospitalization every year across all age groups. 2.5% of the hospitalized patients die from complications associated with the severe form of the disease.[1,2]

Dengue is an arbovirus that has constantly expanded to new areas and territories where control had previously been achieved. Currently, dengue has spread to more than 129 countries, and cases are increasing steadily over time. About 70% of the global burden of the disease is concentrated in Asia. In particular, countries in the Southeast Asian Region are highly affected, with an estimated of 52% of the world's population at risk of becoming ill with Dengue.[2,3]

About half of the planet's inhabitants currently live in environments conducive to the transmission of dengue. Infection occurs through mosquitoes of the Aedes species, which proliferate in tropical and subtropical areas. Combined with these global trends, rising temperatures attributed to climate change have raised concerns that dengue will intensify in already endemic areas through more rapid viral amplification.[4,5]

In the Region of the Americas, it is the arbovirus that causes the greatest number of cases, with epidemics occurring cyclically every 3 to 5 years. In 2019, the highest historical number of notifications was recorded, with more than 3.1 million cases, of which 28,203 were serious with 1,773 deaths. Through to epidemiological week (EW) 52 of 2022, of the 2,803,096 cases reported in the region, 1,299,273 (46.4%), were confirmed by laboratory tests.[3,6]

Since 2020, in endemic countries the circulation of arboviruses including dengue, Chikungunya and Zika occur simultaneously with the active transmission of the SARS-CoV-2 virus. As such, health systems must remain alert to the coexistence of these clinical entities due to the significant effect they may cause on the population.[7]

A complex epidemiological situation has arisen with the identification of new SARS-CoV-2 variants of concern and inadequate coverage with the COVID-19 vaccine. In areas endemic for arboviruses where COVID-19 preventive measures have been relaxed, this has resulted in a high demand on health services, as well as a constant challenge for health systems in all their components and levels, including diagnosis, epidemiological surveillance and management of these cases.[8,9]

The region of the Americas is today a geographical area which has sustained a high impact from arboviruses. This is why the countries of the region have strengthened their health systems for prevention and control, with the establishment of comprehensive clinical, epidemiological, laboratory, entomological and environmental surveillance systems. Cuba does not escape the risk, which is why confronting dengue and other arboviruses is a priority for the country's highest authorities.[8]

Cuba throughout history has shown high levels of Aedes aegypti infestation. Between 1977 and 1978, it reported the first dengue epidemic of the second half of the 20th century. This was caused by the DENV-1 virus and was characterized as an epidemic of dengue fever (DF), with more than 400 thousand cases spread across the country. Sero-epidemiological studies showed that 44.46% of the population was infected by this virus.[9]

In 1981, Cuba reported the first epidemic of Dengue Hemorrhagic Fever (DH) in the region, with more than 300 thousand cases, 10 thousand of these serious with 158 deaths, of which 101 were children. This epidemic, caused by DENV-2, affected the entire country and its transmission was stopped after an intense vector control campaign that lasted 4 months, until its elimination was achieved. The country was free of transmission from 1982 to 1996. In 1997, the Santiago de Cuba municipality reported an epidemic of DHF caused by DENV-2, with more than 5 thousand cases.[10]

In the years 2001-2002, a new DH epidemic occurred, caused by DENV-3, which greatly affected the City of Havana. This epidemic, which began in June 2001, was preceded by a small outbreak due to DENV-3 and 4 in health areas of the Boyeros, Playa and Lisa municipalities at the end of 2000.[8]

In 2005, three small outbreaks of DENV-3 and 4 that occurred in Havana City and Camagüey were eliminated in a timely manner. In 2006, an epidemic occurred, controlled at the beginning of 2007, while in the period 2007-2022, several outbreaks were recorded throughout the country, with circulation of several viral serotypes.[9,10] The present

research aims to characterize hospitalized patients with clinical suspicion of dengue from a clinical, epidemiological and hematological point of view.

METHODS

A descriptive, cross-sectional investigation was carried out at the "Amalia Simoni" Provincial Hospital in Camagüey, Cuba, during the year 2022. The sample was made up of 157 hospitalized patients with clinical suspicion of dengue, selected using the eligibility criteria.

Inclusion criteria

- Patient with a presumptive diagnosis of dengue at the time of admission and a definitive diagnosis during hospital discharge.
- Patient aged 19 years or older.

Exclusion criteria

- Patient re-discussed due to presenting a diagnosis other than the clinical suspicion of dengue raised during hospitalization.
- Patient with incomplete medical history, when it was impossible to consult the values of the variables at the different cut-off points evaluated in the study.

The variables were the following:

- Age group (19-29, 30-39, 40-49, 50-59, 60-69 and ≥70).
- Sex (male and female).
- Month of diagnosis (January, February, March, April, May, June, July, August, September, October, November and December).
- Hematological variables (hematocrit, hemoglobin, platelets and leukocytes).
- Day of hospital stay (1,2,3,4,5,6 and 7).
- Differential formula (polymorphonuclear cells, lymphocytes, eosinophils and monocytes).

The reference values for hematocrit in men are between 0.41-0.54 and in women, 0.37-0.47. The normal global leukocyte count should range between 5-10 x 10e9/L, the platelet counts between 150-450 x 10e9/L and polymorphonuclear cells between 0.55-0.65. Similarly, the reference numbers of lymphocytes are between 0.25-0.35; monocytes between 0.03-0.06 and eosinophils between 0.02-0.04.

The statistical registry and the patients' medical records were the source of information. The data was entered into an Excel database for processing, obtaining absolute numbers and percentages. The results were presented in the form of texts and a comparison was made with those achieved by national and international authors, which allowed conclusions to be reached. Descriptive statistics were applied to obtain absolute numbers and percentages.

The study was approved by the Ethics Committee and the Scientific Council of the "Amalia Simoni" Provincial Hospital of Camagüey. The confidentiality of the data was maintained by coding the variables, accessible only to the researchers, and used for scientific purposes. The bioethical principles contained in the Helsinki Declaration were taken into account.[11]

RESULTS

Table 1 shows the group of 40-49 years of age with the highest prevalence of cases (28.7%), while the group with the lowest incidence was those ≥70 years of age. There was a discrete preponderance towards males compared to females (79:78, respectively).

Table 1. Distribution of patients with dengue according to age group and sex.

Age group (years)	Sex				Total		Measures	
	Female		Male					
	No.	%	No.	%	No.	%	Average	SD
19-29	17	10.8	18	11.5	35	22.3	23.4	5.12
30-39	5	3.2	10	6.4	15	9.6	34.2	4.98
40-49	27	17.2	18	11.5	45	28.7	43.6	5.22
50-59	18	11.5	17	10.8	35	22.3	56.1	5.34
60-69	9	5.7	10	6.4	19	12.1	64.7	4.78
≥70	2	1.3	6	3.7	8	5	76.6	5.67
Total	78	49.7	79	50.3	157	100	49.8	6.03

Source: Patients' clinical chart

Regarding the total number of cases by month, figure 1 shows an increase in the month of March (24), with a decrease in the months of April and May, and then experiencing a sharp drop in the month of June (3). The highest notification of cases occurred in the month of August (33), while the remaining four months had similar behavior.

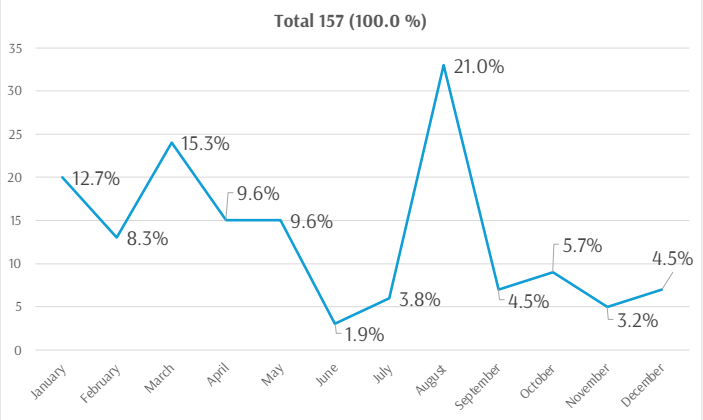

Fig. 1. Distribution of patients with dengue according to month of diagnosis.

Source: Patients' clinical chart

The main signs and symptoms (Figure 2) were represented by fever in 90.4% of cases, followed by headache (59.9%) and arthralgia (50.3%). Abdominal pain was the most prominent warning sign (16.6%). Most of the patients presented more than one symptom or sign.

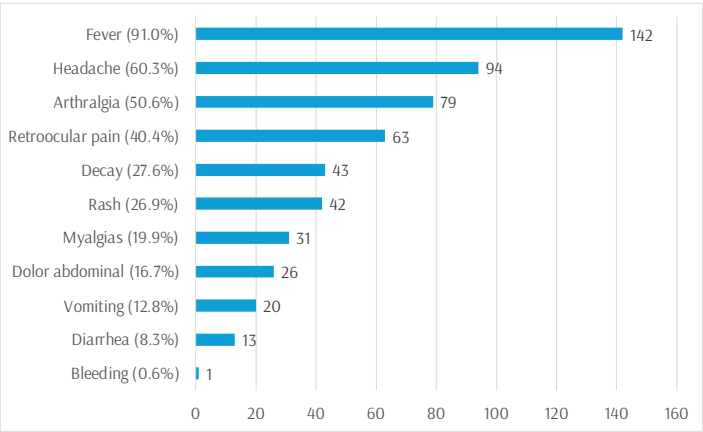

Fig. 2. Distribution of dengue patients according to signs and symptoms.

Source: Patients' clinical chart

Table 2 analyzes the average of the main hematological variables. Hematocrit reached the lowest values during the first day of hospital stay and the highest values on the seventh day. Hemoglobin remained with minimal variations during the course of the seven days of monitoring, while the lowest average platelet count occurred between the third and fourth day, with recovery on the seventh day. Leukopenia became noticeable between the fifth and sixth days.

Table 2. Average values of hematological variables according to days of hospital stay in patients with dengue.

Hematological variables	Day of hospital stay						
	1	2	3	4	5	6	7
	Average						
Hematocrit	0.42	0.43	0.43	0.43	0.43	0.43	0.48
Hemoglobin g/L	13.4	13.5	13.4	13.5	13.6	13.4	13.5
Platelets x 10^9/L	240	231	225	224	230	240	256
Leukocytes x 10^9/L	8.6	7.4	6.2	6.3	5.7	5.8	6.1

Source: Patients' clinical chart

Regarding the differential formula (Table 3), during the first day of hospital stay, the polymorphonuclear cells reached the maximum level (0.72), reaching normal numbers on the seventh day. Lymphocytes were lower during the first day and then remained stable; eosinophils showed no changes, while monocytes increased on the sixth day.

Table 3. Average values of the leukocyte differential formula according to days of hospital stay in patients with dengue

Differential formula	Day of hospital stay						
	1	2	3	4	5	6	7
	Average						
PMN	0.72	0.66	0.67	0.62	0.64	0.62	0.62
Lymphocytes	0.28	0.33	0.34	0.36	0.36	0.36	0.35
Eosinophils	0	0	0.01	0.01	0.01	0.01	0
Monocytes	0.01	0.03	0.03	0.04	0.04	0.05	0.02

Source: Patients' clinical chart

PMN: Polymorphonuclear

DISCUSSION

The epidemiological history and clinical manifestations are of relevance to establish the presumptive diagnosis of dengue. Hematological examinations complement the diagnostic orientation and allow a better follow up of the cases.

In relation to age, similar results were found by authors such as Adane and Getawa,[12] Araya and Wilson,[13] and Khan et al.[14] In this same aspect, García Gómez et al,[15] identified the group of 41-50 years as the most representative, while the predominant sex was male with very discrete difference.

Similar results were found in the present investigation.

Other authors,[15,16] also found a higher prevalence of infection in men. It is the opinion of those responsible for this research that it may be due to cultural habits, where men often take off their shirts during the hot summer months and spend the entire night exposed to mosquito bites.

The month with the highest frequency of cases was August, a result that matches with that obtained by Khan et al.[14] in Pakistan. Garcia et al.[15] state that the risk of dengue infection is influenced by rainfall, temperature and the degree of urbanization.

In the opinion of the authors of the study, the highest incidence of dengue in the month of August could be related to the temperatures and humidity that favor the reproduction of the vector, in addition to abundant rainfall. Due to frequent power outages in the summer months due to high demand, people store water in various containers that serve as larval breeding habitats, resulting in an increase in mosquito population density.

Fever is a clinical manifestation that accompanies a large number of diseases, highlighting infectious diseases, which particularly include dengue. Khan et al.[14] conducted a community-based cross-sectional study where they reported fever and bone pain as fundamental symptoms, followed by headache. Similar results were found in the present series.

In a systematic review[5] on the prevalence and distribution of dengue, reference was made to the high seroprevalence in correspondence with the report of fever, results with which the present investigation coincides. Luque et al.[16] observed in their series of cases that the most frequent clinical manifestations were related to the febrile phase of dengue: fever and systemic symptoms such as headache and nausea.

Hematological disturbances are common in the course of dengue infection, given the pathophysiology of this disease, most frequently found to be a decrease in the number of platelets (thrombocytopenia) and leukocytes (leukopenia), as well as an increase in hematocrit. The appearance of these laboratory findings is frequently reported in various series and usually occur between the third and eighth day of the course of the disease.[17]

When evaluating the evolution and behavior of the values of the hematological variables in the study series in question, it was possible to verify variations that are related to those reported in the literature. Hematocrit is a sign of hemoconcentration secondary to hypovolemia and a variation equal to or greater than 20% with respect to an initial value or a decrease during convalescence with respect to the critical period is considered diagnostic of dengue hemorrhagic fever.[18]

In the literature, a decrease in the number of leukocytes is mentioned as the first abnormality in the blood count. The overall decrease in leukocyte count observed in dengue patients is primarily due to a decrease in the granulocyte population (e.g. neutrophils). The ability of the dengue virus to suppress the production of white blood cells in the bone marrow may explain the appearance of leukopenia.[19]

Leukopenia is usually a common finding in around 68.4% of patients. The differential formula can show neutropenia, especially in the initial phase of the disease. The decrease in total leukocytes begins in the first three days and is slight and, five days after the onset, it is present in the majority of patients; in severe forms of the disease, it is intense and marked. The most notable and characteristic thing in these patients is the differential picture with lymphocytosis and monocytosis.[20]

When the host is infested with the dengue virus, the infection migrates to the lymph nodes. Monocytes and macrophages are recruited, which become the target of the infection, and then amplify and spread through the lymphatic system. As a result of this primary viremia, several cells of the mononuclear lineage, monocytes, myelocytes, and splenic and hepatic macrophages are affected. It is even proposed that the virus has the ability to affect mononuclear cells circulating in the blood.[9]

Platelets are an important blood component involved in clotting. Patients infected with dengue virus tend to develop thrombocytopenia during the course of infection, which makes them vulnerable to hemorrhagic manifestations and other serious complications.[21]

The authors of the current study estimate that platelet counts begin to fall during the febrile stage and reach their lowest point during the toxic stage. The development of thrombocytopenia in dengue infection could be due to bone marrow depression observed in the acute stage of dengue virus infection. Other explanations are direct infection

of megakaryocytes leading to further destruction or the presence of antibodies directed against platelets. Another mechanism is the increase in platelet consumption through interaction with infected endothelial cells. An *in vitro* study demonstrated that some endothelial cells damaged by dengue can promote platelet adhesion and lysis.[21]

Currently, few studies are carried out that include the analysis of hematological aspects in patients with dengue. Its importance is essential for the evolution and monitoring of cases. The main limitation was the impossibility of establishing causal relationships between the dengue event and the variables analyzed, typical of this type of study.

CONCLUSIONS

The sample studied was characterized by the preponderance of patients in the fourth decade of life who presented hyperthermia as the most relevant clinical manifestation. The study of hematological variables was essential for the evolution of the cases.

From a medical perspective, it is recommended to avoid the administration of non-steroidal anti-inflammatory drugs, aspirin or other antiplatelet agents. The patient must stay under a mosquito net and use insect repellents to prevent mosquitoes from becoming infected and infecting other people.

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