A Study on the Clinical and Laboratory Profile of Pediatric Patients with Dengue in a Havana Hospital, Cuba

Daymí Montero Díaz* and Juan Antonio Figueroa Saez

Cerro Pediatric Hospital, Cuba.

Abstract

Dengue is a viral disease, with a wide clinical spectrum. To describe the clinical and laboratory features, and to determine the usual combination of symptoms and signs in pediatric patients who are interned in the Cerro Pediatric Hospital because of Dengue. An analytic, transversal, retrospective study was carried out to a universe of 1300 patients admitted between January and December of 2012, with a sample of 260 patients. The symptoms and signs were studied, also the median of the laboratory values of hematocrit, leukocyte and platelet count were computed. Predictive associations of suffering Dengue according to the age groups were established through the Odds Ratio measure. The more frequently found symptoms were: headache, arthralgia and myalgia, retro-ocular pain, and rash. Laboratory findings only showed a tendency to leukopenia. The predictive combinations of Dengue obtained are: positive fever, rash and loop test for all ages. The fever, rash and arthralgia and myalgia for teenagers (OR= 28,7; CI 95% 3,98-58,3; p= 0,0001) and children (OR= 13,32; CI 95% 1,74-28,0; p= 0,0001); while the fever, headache, retro-ocular pain and rash for teenagers (OR= 9,57; CI 95%; 3,63-26,85; p= 0,00001).In this study the clinic changes with age, does not including respiratory symptoms, but the analyses do not have the same behavior. The association of symptoms and signs must be considered according to the age groups, and those found in teenagers have resulted similar to those reported for adults.

Keywords: Dengue, Febrile Syndrome, Loop Test, Case-Control Study, Dengue Prediction, UMELISA.

Introduction

The Dengue is a viral disease with endemic and epidemic character, and at the same time it is the most important morbid transmitted by arthropods in main form by mosquito *Aedes aegypti,* so it generates a high morbidity and economic cost for health systems [1].

This virus infection has increased worldwide between 1960 and 2010, due to the growth of population, the global warming, the unforeseen urbanization, the inefficient control of the mosquito, the frequent amount of travels, and the lack of a proper sanitaria attention to 500 million of people who live in regions where this entity is endemic. 400 million of infections occur each year, with a mortality index about 5-20% in some areas [2].

Last decades, the OMS has acknowledged and advised the classification of Dengue in: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [3]. In the last years, some authors have questioned the usefulness of this classification, they consider it rigid and too dependent on laboratory results. For this reason, the OMS sponsored an international study called Dengue Control (DENCO), which main goal was to find a better way for classifying the disease. As result of this study, a proposal of a binary classification of the disease was obtained: Dengue and severe Dengue [3-6] (figure 1).

Clinical features of Dengue often depend on the age of the patient. Thus infants and children can suffer an undifferentiated febrile stage, with different kind of rash, e.g. exanthema and morbiliform rash, but for teenagers the recovering time, the fever and the set of symptoms are more intense [3].

One of the main problems of the diagnosis of Dengue is the difficult to early

*Corresponding Author: Daymí Montero Díaz, Cerro Pediatric Hospital, Cuba, Tel: 5358044504, Email: daimim@infomed.sld.cu

Figure 1: Classification of Dengue.
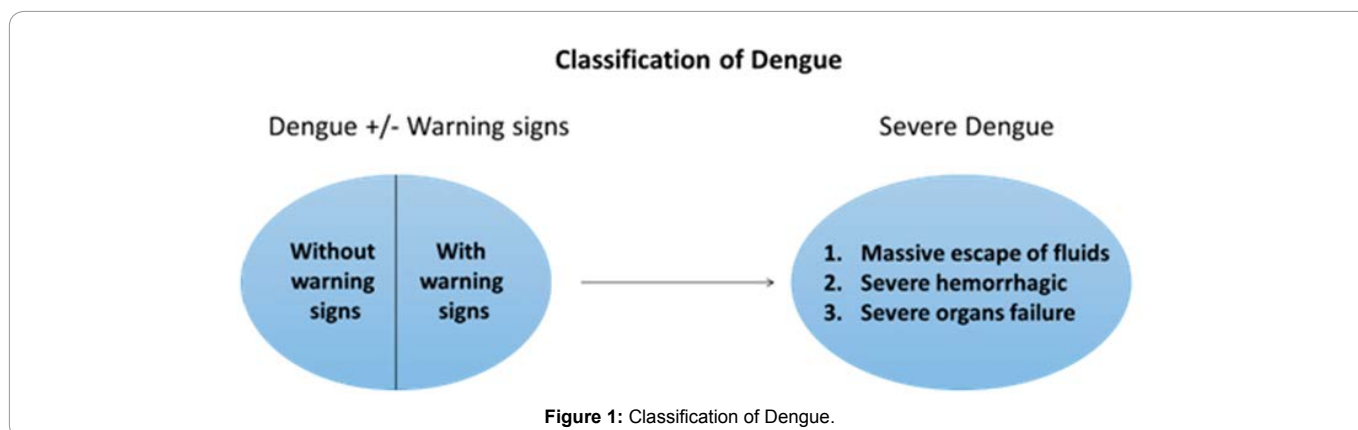
distinguish this arbovirosis (Dengue) from other causes of severe febrile syndrome [7] includes diseases such as influenza, parvovirus B19 infection, gastroenteritis, rubella, leptospirosis, typhoid fever and meningoencephalitis or meningococcemia, which clinical presentation is similar [8], or the other frequently arbovirosis like: Chikungunya and Zika, prevalent common conditions in the tropical countries.

The main objective of this research is to identify the more frequently found combinations of symptoms and signs for patients with positive IgM because: this disease have warning signs and severe damage caused dead in some patients, and one important part of patients admitted in Cuba pediatrician hospital due to the possibility of having Dengue, actually do not have it, neither need internment; this demonstrate the necessity of redefine the internment criteria in order to reduce expenses.

Methods

An analytic, transversal, retrospective study about clinical features of febrile patients which could suffer Dengue was carried out. The patients in the study were admitted in the Cerro Pediatric Hospital, which is the designated institution in Havana, Cuba, for the attention of patients with febrile syndrome between 1 and 18 years-old, in the period of January 1st to December 31st of 2012.

The universe was formed by 1300 patients. At the 6th day of fever on these patients, the IgM test was performed, by using the UMELISA Dengue IgM plus technique, which was developed and produced by the *Centro de Inmuno-Ensayo de la Habana*. When the test result was positive, it contributed to the diagnosis of the clinical cases of infection by some virus of Dengue, due to the epidemiologic situation in that period at Havana, which was characterized by an increase of febrile cases with considerable amount of positive results of the IgM test [9,10].

The computation of the sample was performed according to the following procedure:

1. The sample was computed as function of the universe of patients with positive IgM (1300 patients).

2. The 20% of the universe (260 patients) was chosen, by randomly selecting the first case and then selecting one case each five patients, until obtain the full amount of 260 patients.

3. Later, the patients with negative IgM were randomly selected, for a final sample of 520 patients.

4. Finally, the sample was divided by age as following:

    a) Infants: 1-4years-old

    b) Children: 5-9years-old

    c) Teenagers: 10-18 years-old

For performing this computation, the statistics tool XLSTAT v.9. was used. For all cases in the study, the count of leukocytes and platelet, and the computation of the hematocrit were obtained.

Those febrile patients admitted because of Dengue, between 1 and 18 years-old, were considered for including in the study. While those patients with an incomplete clinical expedient, were automatically excluded.

Methods for the compilation and processing of information

The information for data processing was obtained from clinical history documents and used in a survey registered in a spreadsheet.

To know the possible associations of symptoms and signs, the data mining technique known as decision tree was used, by means of the *Rapid Miner* v.5 tool (freely available with GNU-GPL license) [11-13]. This technique creates a flow diagram with a tree structure, where intern nodes are validations of attributes and branches are classes for extracting the hidden information, i.e. to find a pattern on the data behavior.

In this study, the main variables of the decision tree were symptoms and signs in function of the age groups. The sensibility for predicting positive cases was 91, 52%, and the specificity was moderated (51.52%). In general, the most important variables obtained were the positive test loop and the rash. According to decision tree results, a statistical study was performed for determining the different combinations of symptoms and signs which allow predicting positive cases of Dengue. The following section presents more details on the obtained results.

Once the decision tree was finished, the following clinical association groups of symptoms by age were obtained:

a) Fever + rash + positive loop test

b) Fever + rash + arthralgia and myalgia

c) Fever + headache + retro-ocular pain and rash

Then, to know the risk of suffering the symptoms previously described in the associations, the following measures were computed: Odds Ratio (OR) and Confidence Interval. These measures were statistically validated through chi-square (x^2), with a significance level of p > 0,05, by using the software for statistical processing called STATCALC.

The following clinical variables were analyzed:

- Demographics: Age

- Clinical: Fever (the first day of the fever was considered as the first day of the disease), headaches, rash, retro-ocular pain, diarrhea, vomiting, abdominal pain, respiratory signs and symptoms, arthralgia and myalgia and positive loop test. As all these symptoms are not happening at same time, they were studied during all days of the disease.

- Laboratory: the count of leukocytes and platelet, and the hematocrit index were studied starting from the 3rd day, because this is the usual moment for the typical changes by leukopenia, the platelet index decreases and the hematocrit index increases; and finishing at the 5th day, because usually the patient is release at 6th day, after the extraction of the IgM, if there are not further complications.

Continuous variables were processed using the average as measure of the main tendency. The risk was computed through the ratio of crossed products, i.e. the OR measure, using the x^2, with p ≤ 0,05, for evaluating the statistical significance. Contingency tables and figures were created for results presentation, which main association was based on the age groups and according to the serological result of the IgM, as well as the distribution of the laboratory test results.

Results

The behavior of the signs and symptoms (Table 1). There, the more frequent clinical issues of patients with positive IgM are represented by the fever (100, 0%), which is the most constant sign. This is followed by the headache (50%), the rash (56, 5%), the retro-ocular pain (31, 5%), the arthralgia and myalgia (28, 8%) and the positive loop test (21, 9%). Note that respiratory symptoms are mostly in those patients with negative IgM (40, 7%), as well as the diarrhea (15, 3%). The rash was presented in the 18,4 % of patients. The first table shows that the patients with IgM positive obviously present signs and symptoms representative to the Dengue illness besides expose that the respiratory signs and symptoms are not usually present in the clinical profile of Dengue.

The average value of hematocrits, leukocytes and platelet count from 3rd to 5th day of disease according to IgM results (Table 2). The hematocrit index reaches an average of 38 Vol./% without appreciated variation on the different days and groups. The platelet count does not have considerable oscillation, and its results remain in normal values. On the other side, the total count of leukocytes has a slightly difference, for the cases with positive IgM it has a constant value of 6×10^9 cells/L in the studied period, which indicates a kind of stability to the lower bound. While, the patients with negative IgM have decreasing variations at the 2nd, 4th and 5th day, with medians of 10, 9 and 8×10^9 cells/L respectively. Many authors describe that the hematocrits increase at 3erd days but in this study whit pediatric patients we do not obtain this results.

Results for combination A (fever + rash + positive loop test) are presented in table 3. Note that patients from 1 to 18 years-old with this sign association have more probability of getting a positive IgM, with p≤ 0,001. This is even more meaningful in children, who presented 24 times more risk (CI 3,41-510,37) with p= 0,00001. That means who pediatrics patient by: fever, rash and positive loop test have more risk to present Dengue fever and less possibility to present another disease.

The results for combination B (fever + rash +arthralgia and myalgia) (Table 4). The children between 5 and 18 years old with: fever, rash, arthralgia and myalgia have 13,32 and 28,7 more probability to present Dengue, however the children between 1 and 4 years with the same condition do not have the probability to have it.

Results for the combination C (fever + headache + retro-ocular pain + rash) (Table 5). Results show that the disease in patients older than 10 years-old reached OR = 9,57 (CI 3,63-26,65) with statistical significance. While the other patients have lower OR values and also without statistical significance. These

IgM Qualitative Value	Average								
	Hematocrit (Vol./%)			Platelet (10^9cells/L)			Total count of leukocytes (10^9 cells/L)		
	3rd day	4th day	5th day	3rd day	4th day	5th day	3rd day	4th day	5th day
Positive	38	38	38	234,5	198	199	6	6	6
Negative	38	38	38	204,5	232,5	196	10	9	8

Table 2. Medians of blood and platelet count values for different hospitalization days.

Age groups (years)	+IgM	-IgM	Odds ratio	Confidence interval	Significance level
1-4	12	2	9,14	1,79-62,51	0,001
5-9	20	2	24,93	3,41-510,37	0,00001
10-18	21	1	19,68	2,73- 510,0	0,000008

Table 3. Statistic study of the combination A: fever + rash + positive loop test.

Age groups (years)	+IgM	-IgM	Odds ratio	Confidence interval	Significance level
1-4	2	2	1, 23	0,12-26,2	0,8
5-9	12	1	13, 32	1,74-28,0	0,001
10-18	21	1	28, 7	3,98-58,3	0,000001

Table 4. Statistic study of the combination B: fever + rash +arthralgia and myalgia

Clinical symptoms and signs (N= 520 patients)	Positive IgM #	%	Negative IgM #	%
Fever	260	100,0	260	100,0
Headache	130	50,0	102	39,2
Rash	147	56,5	48	18,4
Retro-ocular pain	82	31,5	30	11,5
Diarrhea	25	9,6	40	15,3
Vomiting	42	16,1	40	15,3
Abdominal pain	45	17,3	22	8,4
Respiratory signs and symptoms	12	4,6	106	40,7
Arthralgia and myalgia	75	28,8	18	6,9
Positive loop test	57	21,9	5	1,9

Table 1. Relationship between the clinical symptoms and signs and the IgM result.

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Age Groups (years)	IgM+	IgM-	Odds ratio	Confidence interval	Significance level
1-4	1	3	0.40	0,02-4,47	0,4
5-9	17	10	1,83	0,74-4,4	0,15
10-18	41	6	9,57	3,63-26,65	0,0000

Table 5. Statistic study of the combination C: fever + headache + retro-ocular pain + rash.

figures indicate that this combination has more probability to present signs and symptoms with positive IgM for patients older than 10 years-old.

Discussion

Regarding to the clinical framework, the single symptom form of the disease was most evidenced, the variable intensity fever is the more constant sign for all cases, sometimes this could be the only sign presented. Other symptoms like the rash, the headache, the retro-ocular pain, the arthralgia and myalgia and the positive loop test, are observed in a higher amount of patients with positive IgM, which is consistent with previous results [14,15].

For children, often the fever is the only clinical expression, or this comes together with digestives disorders, such as diarrheas and lower intensity abdominal pain for infant patients (younger than 2 years-old) [16]. Also results have shown that respiratory symptoms and signs are not frequent, except that they are the expression of an associated disease [17]. If this is the case, it must be carefully revised due to the consequences that it could bring over the diagnosis of Dengue [18].This found is consistent with results, which gives value to the lack of runny nose in the predictive scale for performing the diagnosis of Dengue [19]. The usual symptoms of Dengue are fever, retro-ocular pain, osseous-articular pain and rash [7]. The 33 patients (i.e. 83.3% of the sample) have presented fever associated with rash, in a study on the skin issues of Dengue [20].

The rashis also a usual sign for all ages [21]. The raising of rash in the 50-80% of patients [21]. This rash has different characteristics ranging from an exanthema to a morbiliform rash, which force the medical doctor for performing a wide differential diagnosis [2].

In this research the positive loop test was the common factor for patients with positive IgM. This provides another diagnosis tool to the medical doctors, for detecting and infection provoked by this arbovirus. This sign is included in the Cuban Guides for the attention of patients with Dengue [22]. Other studies performed with this test are mainly focused on the prediction of bleeding with different results. The positive loop test shows double of possibility of suffering spontaneous bleeding in patients diagnosed with Dengue (DEN-2), regarding those with the negative loop test [23]. The test actually has low sensibility for distinguishing severe Dengue in its hemorrhagic form [24].

Regarding the laboratory results such as hematocrit, platelet count and count of leukocytes, there are not meaningful parameters alteration or variation, they have normal values. Only the count of leukocytes has tendency to leukopenia, but without actually reach it in the studied period. There are not evidences of hemoconcentration or fall of platelets between 3rd and 5th day of disease. This could be associated with the fact that these issues are more frequently found on patients who have warning signs

in their evolution, however in this study there was not any case like this.

The classic biometric profile of Dengue shows leukocytes figures lower than 4500/mm^3, a prevalence of lymphocytes, with non-typical lymphocytes (until 10%) and late eosinophilia [25].

Usually, the leukopenia is normalized around the 10th day. If there are not any coexistent infections or another explanation factor, the leukocytosis ≥ 6 000 mm^{3}is associated to severe forms or an inaccurate diagnosis. Frequently there is decrement of the platelet count. The raised hematocrit index (≥ 20%) over the average value corresponding to the age and population is indicating hemoconcentration.

The study shows that how to predict the severe Dengue from this entity with warning signs [26]. They did not report any difference for the hematocrit or white blood cells index, however, they did report differences in the mean of the platelet count in 3rd, 4th, 5th and 6th day of disease.

About the combinations of the clinical manifestations according to the age for predicting febrile patients with positive IgM, the combination A shows that all age groups have risk, mainly for children and teenagers. This is influenced by the predictive value of the positive loop test (80% of sensibility) [27].

The combination B results are similar which presented the rash and the arthralgia and myalgia as usual symptoms and signs for patients older than 10 years-old [28]. The same phenomenon, either for teenagers as for patients between 5 and 9 years-old [29].

During this study the arthralgia and myalgia were mainly observed on children and teenagers. We do not think that is indicating a lack of arthralgia and myalgia on infants, but the low of possibility for identifying and describing this symptom, because it is actually difficult to detect on infants younger than5 years-old. Sometimes, this fact induces medical doctors and parents to predict its presence on a crying and uneasy infant, who prefer to rest in bed instead to walk or play games.

The combination C, found in usual way for teenagers, is similar to the clinical framework described by several authors [3,7,30,31]. During the Dengue epidemic in adults, in Paraguay, in 2007, reports that the main clinical symptoms and signs were: fever for all cases, headache for 258 patients (87, 2%), retro-ocular pain for 236 (79, 7%), osseous and muscle pain for 244 (82,4 %) [32]. These symptoms are very similar to those observed on teenagers in this study.

The description of these associations and the differences between the age groups should be considered for performing the clinical diagnosis of this entity in Pediatric. These could follow the singularities of children in the different development stages.

This work has limitations related to the serological aspect and the age. About the serological aspect, there is the issue of does not have an exact knowledge about presence of secondary Dengue; in the case of there is not performed the IgM test in the sample, at 6th day the IgM could be negative and latter it could became positive. About the age, this study did not include baby patients (younger than 1 year-old), because they are usually attended in a different hospital.

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Although the Dengue is only one disease, this does not usually occur in the same way for different ages. This could be due to the previous exposition of the patient to any serotype of virus Dengue, where the amplification phenomenon carries out that teenager have more symptomatic expressions, added to the difficult for showing this illness on kids. For achieving solid conclusions, each case should be analyzed in a framework where social and epidemiologic factors are considered.

Conclusion

This study concludes that pediatric patients present varied clinical profile according to the age, the associations of symptoms and signs must be considered according to the age groups were found similar associations of symptoms and signs for teenagers with those reported on adults. There is not observed respiratory symptoms, neither meaningful variation on laboratory findings, on the clinical framework.

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