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Research Article

Clinical and Laboratory Behavior of Dengue in Children Hospitalized in 2 Epidemics. Period 2012 - 2013 and 2017 - 2018

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Abstract

Introduction: Dengue fever which has different forms of clinical presentation, changing epidemiology, is currently characterized by an increase in the number of cases, hospitalizations and death in the pediatric age group.

Objective: To compare the clinical and laboratory behavior of dengue infection in hospitalized children and to identify prognostic factors of severity and mortality in two pediatric reference centers of Paraguay in two periods (2012 - 2013 and 2017 - 2018).

Materials and Methods: Prospective, longitudinal, observational study, obtaining clinical, demographic, laboratory data and evolution of patients from six months to 17 years of age, with a confirmed diagnosis of dengue.

Results: Of 217 patients, 178 (95 of the 2012 - 2013 epidemic and 83 of 2017 - 2018) met the inclusion criteria. In the second period, there was a significant (p = 0.01) greater affection in children under 5 years (RR = 1.87, 95% CI: 1.14 - 3.05), higher frequency of respiratory symptoms such as cough (p = 0.001; RR = 3.6 CI 95%: 1.6 - 8.0) and rhinorrhea (p = 0.001, RR = 5.2 CI 95%: 2.2 - 11.9) and higher frequency of gastrointestinal symptoms such as diarrhea (p value < 0.001, RR = 4.0 CI 95%: 1.7 - 9.4). The mortality rate (< 2%) was similar in both epidemics. The hematocrit (41.0 ± 7.7 vs. 38.8 ± 4.7, p: 0.021 and the platelet count (140.676 vs. 178.642), p = 0.001) for the period 2017 - 2018 vs 2012 - 2013 respectively. Risk factors associated with mortality were: presence of ascites, pleural effusion, alteration of APTT, AST, ALT, fibrinogen and admission to PICU.

Conclusion: Identify respiratory symptoms, gastrointestinal and risk factors associated with mortality: presence of ascites, pleural effusion, alteration of APTT, ALT, AST, fibrinogen and admission to PICU, can contribute to the diagnosis and timely treatment of dengue.

Keywords: *Dengue; Epidemic; Clinical and Laboratory Characteristics; Paraguay*

Introduction

Dengue is a viral disease caused by any of the four serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) of the virus belonging to the Flaviviridae family. It is transmitted by mosquitoes, particularly Aedes aegypti, and predominates in tropical and subtropical areas and in urban areas [1,2].

In the last two decades, there has been a dramatic increase in the global incidence of Dengue. The World Health Organization (WHO) estimates that more than 2.5 billion people live in areas at risk of contracting the disease, and it is estimated that more than 50 million cases occur each year, and approximately 24,000 deaths, mainly in the pediatric population [3].

Infection with the Dengue virus results in syndromes that vary in severity and prognosis, and includes febrile dengue, dengue hemorrhagic fever, and dengue shock, the latter being the most severe form of the disease. The clinical manifestations of dengue vary from a non-specific febrile disease to a more severe form with hemorrhage, thrombocytopenia and plasma extravasation, which can lead to death. In children, dengue may be asymptomatic or polysymptomatic, which may hinder the differential diagnosis [4].

In Paraguay, dengue has become a major public health problem in recent years. The first dengue epidemic was registered in the period 1988-1989 with the circulation of DEN-1 and with a total notification of 41,990 cases throughout the country. In 2010, confirmed cases reached 13,766, with circulation of serotypes DEN-1, 2 and 3 [5]. Between 2011 and 2012, 42,264 cases were confirmed, with serotypes DEN 1 and DEN 2 circulating simultaneously in 2011, and DEN-2 and DEN-4 in 2012 [6]. Between December 2012 and July 2013, 12,014 (10%) and 113,572 (90%) were confirmed by epidemiological link [7].

A study conducted in the pediatric population in the Pediatric Service - Institute of Tropical Medicine on the increase in the severity of dengue in children in three successive epidemics: years 2007, 2009 and 2011 in Paraguay show that during outbreaks caused by DENV-3 and DENV-2 increased frequency of severe cases (including cases with visceral involvement) was observed compared to the outbreak caused by DENV-1. The incidence of visceral complications (encephalitis/myocarditis/hepatitis) was greater in the outbreaks 2011 (54/123, 44%) and 2007 (24/98, 24%) compared to 2009-10 (5/49.10%) ($p < 0.01$), as well as the frequency of severe hemorrhage [18/123 (14.6%) in 2011 vs 1/49 (2%) in 2009/10, $p < 0.05$ and thrombocytopenia < 50000 29% in 2011 vs. 12% in 2009/10, $p < 0.05$). The mortality rate was similar in the three periods (1%, 2% and 1.6%) [8,9].

Currently, there is no authorized or antiviral vaccine against dengue. Treatment for patients with suspected dengue is supportive consisting of rehydration and antipyretics [3]. Patients with suspected dengue are often hospitalized for better management. The plasma loss occurs around the time of the defervescence. Prior to this critical phase, it is difficult to differentiate between mild and severe disease. Ideally, only severe cases should be hospitalized. However, there are no diagnostic/prognostic tools available to distinguish severe dengue from non-severe dengue or other febrile diseases in the early stages of the disease. Such tools could improve clinical practice by decreasing the number of unnecessary hospitalizations, improving the use of limited hospital resources to treat more seriously ill patients, improving the outcomes of seriously ill patients by administering the necessary care earlier and improving the ability of physicians in rural areas to make a more accurate early diagnosis. Hence the importance of characterizing cases of dengue in our service. The objective of this study is to compare the clinical and laboratory behavior of dengue infection in hospitalized children and to identify prognostic factors of severity and associated mortality in two pediatric referral centers of Paraguay in two non-consecutive epidemics 2012 - 2013 and 2017 - 2018.

Methodology

Design, place and period of study

Prospective, longitudinal, observational study.

Inclusion criteria

Children between six months and 17 years of age with a temperature ≥ 38°C for no more than 72 hours without apparent focus who attended 2 reference pediatric institutions, for consultation and were hospitalized and monitored up to 24 hours after the defervescence in two periods 2012 - 2013 and 2017 - 2018 until March.

The confirmation of the diagnosis of dengue was made by laboratory methods and was defined by the presence of the dengue NS1 positive test or by the detection of DENV RNA in plasma by reaction of the PCR polymerase chain (CPR molecular biology).

The fluid management (oral rehydration or intravenous fluid) was performed by the ward doctor according to clinical need.

Data collection

The data were collected in a pre-designed form in which demographic data, clinical data [duration of fever, as well as associated signs and symptoms (body pain, gastrointestinal symptoms, hemorrhagic manifestations, abdominal pain, hypotension, among others) were recorded)] and laboratory data [hematocrit, platelet count, fibrinogen, APTT, hepatic enzymes (ALT/AST)]. The variables related to patient evolution (admission to the ICU, survival/mortality) and complications (organ involvement, ascites and pleural effusion) were also recorded. Likewise, patients were classified according to the latest World Health Organization Dengue classification guide of 2009 that classifies patients as cases of Dengue with or without signs of alarm and cases of severe dengue.

Statistic analysis

The demographic, clinical and laboratory information of the patients was stored in an electronic database (Microsoft Excel 97, Microsoft Corp.) and analyzed by the statistical package Epi-Info 2000, version 1.1 (Centers for Disease Control and Prevention, Atlanta, GA).

The ANOVA statistical test was used, a way to compare the means of laboratory results and vital signs at different times of the patient's evolution. To identify possible prognostic factors for severity, the chi-square test and logistic regression were used, considering statistical significance when the value of $p < 0.05$.

Results

Of 217 patients with febrile syndrome, 178 patients (95 patients from the 2012 - 2013 epidemic and 83 from 2017 - 2018) met the inclusion criteria (with antigenaemia or positive serology for dengue). significantly (p value = 0.01) greater affection in children under 5 years old (RR = 1.87 IC95%: 1.14 - 3.05), higher frequency of respiratory symptoms such as cough (p value = 0.001; RR = 3.6 95% CI: 1.6 - 8.0) and rhinorrhea (p value = 0.001, RR = 5.2 IC95%: 2.2 - 11.9) and higher frequency of gastrointestinal symptoms such as diarrhea (p value < 0.001; RR = 4.0 IC95%: 1.7 - 9.4) in the 2017 - 2018 epidemic compared to the 2012 - 2013 epidemic (Table 1). Of the 53 patients who had flu symptoms (cough and/or rhinorrhea), 47 were tested for a respiratory virus (Influenza A and B-Adenovirus and RSV), only two were positive for influenza, negative for the other viruses. Test for immunochromatography.

Clinical and demographic characteristics	Year 2013 n: 95	Year 2018 n: 83	Total n = 178	Value p	RR
Under 5 years	19 (20.0%)	31 (37.3%)	50 (28.1%)	0.010	1.87 (1.14 - 3.05)
Febrile	93 (97.9%)	77 (92.8%)	170 (95.5%)	0.100	
Hemorrhage	27 (28.4%)	24 (28.9%)	51 (28.7%)	0.942	
Cough	7 (7.4%)	22 (26.5%)	29 (16.3%)	0.001	3.6 (1.6 - 8.0)
Rhinorrhea	6 (6.3%)	27 (32.5%)	33 (18.5%)	< 0.001	5.2 (2.2 - 11.9)
Diarrhea	6 (6.3%)	21 (25.3%)	27 (15.2%)	< 0.001	4.0 (1.7 - 9.4)
Arthralgias	5 (5.3%)	5 (6.0%)	10 (5.6%)	0.826	
Severe abdominal pain	5 (5.3%)	5 (6.0%)	10 (5.6%)	0.826	
Intense headache	4 (4.2%)	8 (9.6%)	12 (6.7%)	0.150	
Hepatitis	2 (2.1%)	0	2 (1.1%)	0,537	
Seizure	1 (1.1%)	4 (4.8%)	5 (2.8%)	0.129	
Ascites	4 (4.2%)	4 (4.8%)	8 (4.5%)	0.845	
Pleural effusion	5 (5.3%)	5 (6.0%)	10 (5.6%)	0.826	
Dengue fever group B1	28 (29.5%)	27 (32.5%)	55 (30.9%)	0.660	
Dengue fever group B2	67 (70.5%)	56 (67.5%)	123 (69.1%)		
Decompensated shock	5 (5.3%)	5 (6.0%)	10 (5.6%)	0.826	
PICU	5 (5.3%)	5 (6.0%)	10 (5.6%)	0.826	

Table 1: *Clinical and demographic characteristics of dengue fever in children in two epidemic outbreaks 2012 - 2013 and 2017-2018 in Paraguay.*

In relation to laboratory parameters, the average value of the hematocrit at admission was significantly higher in the epidemic of 2017 - 2018 (41.0 ± 7.7 vs 38.8 ± 4.7, p: 0.021). The 2017 - 2018 epidemic was significantly (p = 0.001) lower than in 2012 - 2013 (178,642 vs. 140,676).

The platelet count less than 100 thousand on admission was in 17.9% of cases in the 2012 - 2013 epidemic and 31.3% in the 2017 - 2018 epidemic. In both epidemics, more than 80.0% of the patients were discharged with platelet counts of 100 thousand or more (Table 3).

Tables 4 and 5 show the prognostic factors of severity, finding that patients who presented ascites, pleural effusion, fibrinogen and altered APTT were significantly more likely to enter PICU and have a fatal outcome.

		Year	Mean ± SD	Minimum	Maximum	Value p
Hematocrit	Entry	2013	38.8 ± 4.7	22	52	0.021
		2018	41.0 ± 7.7	8	64	
		Total	39.8 ± 6.3	8	64	
	2nd	2013	36.2 ± 3.9	Twenty-one	47	< 0.001
		2018	38.6 ± 4.5	22	51	
		Total	37.3 ± 4.4	Twenty-one	51	
	3rd	2013	36.0 ± 4.3	25	49	0.150
		2018	35.0 ± 4.4	29	49	
		Total	35.5 ± 4.4	25	49	
	4th	2013	34.7 ± 4.4	29	49	< 0.001
		2018	37.4 ± 4.2	28	49	
		Total	35.9 ± 4.5	28	49	
Platelets	Start	2013	178,642 ± 78,732	15,000	457,000	0.001
		2018	140,676 ± 72,427	14,800	389,000	
		Total	160,939 ± 77,993	14,800	457,000	
	1st	2013	163,463 ± 76,955	20,000	480,000	0.969
		2018	163.892 ± 67.379	13,000	360,000	
		Total	163,663 ± 72,445	13,000	480,000	
	2nd	2013	162.842 ± 65.201	13,000	360,000	0.026
		2018	185.301 ± 68.385	28,000	360,000	
		Total	173,315 ± 67,457	13,000	360,000	
	3rd	2013	176.168 ± 66.106	28,000	360,000	0.910
		2018	177.301 ± 67.352	23,000	360,000	
		Total	176,697 ± 66,503	23,000	360,000	
	4th	2013	176.579 ± 65.825	23,000	360,000	0,698
		2018	172,318 ± 80,514	12,500	596,000	
		Total	174,592 ± 72,862	12,500	596,000	

Table 2: *Comparison of laboratory parameters among children hospitalized for dengue between two epidemic outbreaks (2012-2013 and 2017-2018) in Paraguay.*

Platelets	2013			2018		
	Final			Final		
Start	< 100mil	≥ 100mil	Total	< 100mil	≥ 100mil	Total
< 100mil	3 (17.6)	14 (82.4)	17 (17.9)	4 (15.4)	22 (84.6)	26 (31.3)
≥ 100mil	11 (14,1)	67 (85.9)	78 (82,1)	2 (3,5)	55 (96.5)	57 (68.7)
Total	14 (14.7)	81 (85.3)	95	6 (7.2)	77 (92.8)	83

Table 3: *Paired comparison between two epidemic outbreaks (2012 - 2013 and 2017 - 2018) of platelet counts at the beginning and at the end of follow-up in children hospitalized for dengue in Paraguay.*

Prognostic factors		PICU (n = 10)	NO PICU (n = 168)	Value p
Ascites	Yes (n = 8)	8 (100%)	-	< 0.001
	No (n = 170)	2 (1.2%)	170 (98.6%)	
Pleural effusion	Yes (n = 10)	10 (100%)	-	< 0.001
	No (n = 168)	-	168 (100%)	
Fibrinogen	Altered (n = 10)	10 (100%)	-	< 0.001
	Normal (n = 168)	-	168 (100%)	
APTT	Altered (n = 10)	10 (100%)	-	< 0.001
	Normal (n = 168)	-	168 (100%)	
ALT	Altered (n = 15)	10 (66.7%)	5 (33.3%)	< 0.001
	Normal (n = 163)	0	163 (100%)	
AST	Altered (n = 15)	10 (66.7%)	5 (33.3%)	< 0.001
	Normal (n = 163)	0	163 (100%)	

Table 4: *Prognostic factors of severity in children hospitalized for dengue in paraguay.*

Prognostic factors		Death (n = 5)	Live (n = 173)	RR	Value p
PICU	Yes (n = 10)	3 (30.0%)	7 (70.0%)	25.2 (4.7 - 134.1)	< 0.001
	No (n = 168)	2 (1.2%)	166 (98.8%)		
Ascites	Yes (n = 8)	2 (25.0%)	8 (75.0%)	14.2 (2.6 - 132.5)	< 0.001
	No (n = 170)	3 (1.8%)	167 (98.2%)		
Pleural effusion	Yes (n = 10)	3 (30.0%)	7 (70.0%)	25.2 (4.7 - 134.1)	< 0.001
	No (n = 168)	2 (1.2%)	166 (98.8%)		
Fibrinogen	Altered (n = 10)	3 (30.0%)	7 (70.0%)	25.2 (4.7 - 134.1)	< 0.001
	Normal (n = 168)	2 (1.2%)	166 (98.8%)		
APTT	Altered (n = 10)	3 (30.0%)	7 (70.0%)	25.2 (4.7 - 134.1)	< 0.001
	Normal (n = 168)	2 (1.2%)	166 (98.8%)		
ALT	Altered (n = 15)	3 (20%)	12 (80%)	16.3 (2.9 - 90.1)	< 0.001
	Normal (n = 163)	2 (1.2%)	161 (98.8%)		
AST	Altered (n = 15)	3 (20%)	12 (80%)	16.3 (2.9 - 90.1)	< 0.001
	Normal (n = 163)	2 (1.2%)	161 (98.8%)		

Table 5: *Prognostic factors of mortality in children hospitalized for dengue in Paraguay.*

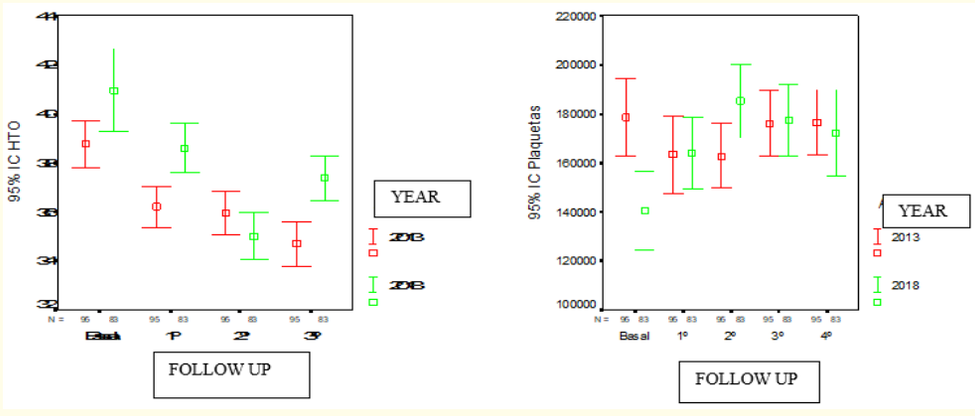

Figure 5: *Comparison of laboratory parameters among children hospitalized for dengue between two epidemic outbreaks (2012 - 2013 and 2017 - 2018) in Paraguay.*

Discussion

Dengue is a systemic and dynamic infectious disease. It can be asymptomatic or manifest with a broad clinical spectrum, which includes serious and not serious manifestations [10]. The patient's condition influences the evolution of the disease, among which the extremes of life (less than 1 year) are considered a risk factor for severity [11-13]. In our study of the 2 epidemics, there was involvement of patients under 5 years of age and in a higher percentage in the 2017 - 2018 epidemic, reaching 37.3%. This result is comparable to that found in Paraguay by Cuellar., *et al.* [14] in the period 2010-2013 who observed the highest frequency of hospitalization in the age group < 1 year (591/3475, 17%), 1 to 4 years (6.5%) and 5 to 14 years (5687/42455; 13.4%). The study Agarwal., *et al*. in India [15], they show that 54% of hospitalized children were in the group between 5 to 10 years of age, and 4% were less than one year.

It should be noted that fever did not occur in all patients, unlike Waydande., *et al.* [16], who reported it in 100% of the cases. This result shows that patients with dengue can present afebrile and with atypical manifestations of the disease such as respiratory, gastrointestinal, renal and hepatic involvement as described by other authors [17,18].

Among the gastrointestinal symptoms, diarrhea occurred in 15.2%, with a significant increase in the 2017 - 2018 epidemic, from 6.3% (6/95) to 25.3% (21/83). This situation has been previously described [17].

It is important to note the presence of respiratory symptoms (cough and influenza) in both periods, being significantly higher in 2017 - 2018, observed in this period in 55.4% of patients. These symptoms have already been described by Malavige., *et al.* [18], it should be taken into account because it may affect more infants where coryza may be the predominant symptom [17,19,20]. All the patients who had respiratory symptoms were given laboratory profile of respiratory viruses to rule out co-infection, all of them were negative except two patients.

Severe complications of the disease such as hepatitis and seizure occurred in a lower percentage in both periods, there were 2 cases of hepatitis in the 2013 epidemic, both initiated as dengue. These manifestations were previously described as atypical cases; and can appear from the early stages of infection by direct action of the virus, by apoptosis or by other mechanisms leading to death [21,22]. In the study by Araya., *et al.* the incidence of visceral complications (encephalitis/myocarditis/hepatitis) was greater in the outbreaks of 2011 (54/123, 44%) and 2007 (24/98, 24%) compared to 2009-10 (5/49.10%) ($p < 0.01$).

The frequency of patients with dengue with alarm signs belonging to group B2 was similar in both periods, 70% and 67.5%, respectively. Similarly, the frequency of patients with decompensated shock 5.3% and 6%, respectively. In one study, 47.7% (52/110 cases) and 23.63% (26/110 cases) of dengue B2 and severe dengue respectively were recorded [19].

5.6% of the patients required admission to the PICU, being similar in both periods. The mortality rate was 1.7%, no significant difference being observed in both periods. This result is similar to the 1% reported by Agarwal., *et al*. in India in the epidemic of 2015, and in the three periods reported in Paraguay by Araya., *et al.* [9], who found 1%, 2% and 1.6% in the outbreaks of 2007, 2009 - 2010 and 2011, respectively. It should be noted at this point that the authors concluded that during the circulation of DENV-3 and DENV-2 there was a greater frequency of severe cases including greater visceral involvement.

In our study, the presence of hemorrhage was similar in the two periods, 28.4% in 2012 - 2013 and 28.9% in 2017 - 2018. In the study by Araya., *et al.* [9], the frequency of severe hemorrhage was significantly higher ($p < 0.05$) in 2011 with 14.6% (18/123) of the cases compared to 2% (1/49) in the 2009/10.

Regarding the laboratory results, the average values of the Hto on admission were higher in 2018, with a difference in significance as well as the 2nd and 4th days, however with a greater decrease in the 2013 period. Haemoconcentration was considered when a Hto of more than 20% of the baseline was documented, this is associated with greater severity of the disease, the degree of increase of the hematocrit faithfully reflects the importance of the plasma leakage and serves as a guide for the replacement of fluids, Perhaps the explanation may be that patients of the period 2018 have presented a picture of more plasma capillary leak. However, in the study by Lovera., *et al*. [23], when Hto has been explored as a risk factor for shock, it was not significantly associated with the development of shock (1.4, 95% CI: 0.9 - 2.1, P = 0.1) We had a hematocrit greater than 40% as observed at the beginning of the 2018 period compared to a report [24], but on the other hand, the percentage of hematocrit found in another study was much lower: 34.9 ± 5.6 in patients with dengue with or without warning signs and 33.4 ± 7,8 in severe dengue [15]. Ratageri., *et al.* [25], observed values of hematocrit > 35% in 50% of children and in the study by Dhooria., *et al*. [26] the mean hematocrit was 35.5% ± 3.92.

The platelet count less than 100 thousand on admission was in 17.9% of cases in the 2012 - 2013 epidemic and 31.3% in the 2017 - 2018 epidemic. In both epidemics, more than 80.0% of the patients were discharged with platelet counts of 100 thousand or more. The decrease in platelets is observed at the beginning of the critical phase of the disease, it is also associated with plasma viral load, it has also been correlated with plasma leakage and hemorrhage in the evolution according to some authors [19,27,28]. Thrombocytopenia < 50,000 was observed in 29% in 2011 vs. 12% in 2009/10, $p < 0.05$) in the study by Araya., *et al* [9].

In our study, critical patients who required admission to the PICU and those who died, all had ascites and pleural effusion and the altered values of fibrinogen, APTT, hepatic transaminases, which consolidates these clinical and laboratory characteristics as prognostic factors of severity. coinciding these findings with some authors [23-30].

Conclusion

In conclusion, atypical manifestations of dengue are no longer rare entities, therefore treating physicians especially pediatricians should have a high degree of suspicion and surveillance of these manifestations of dengue, as the lack of timely detection and management can be fatal.

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