Primary Dengue Infection in Patients Requiring Hospitalization During an Outbreak in a Low Incidence Mexican Region

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Abstract

Background: Dengue manifestations can range from subclinical to fatal. The study of factors that influence dengue's clinical severity can provide information to potentially limit or predict severe cases. Secondary infection (SI) with a different dengue serotype has been recognized as an important determinant of severity. However, severe dengue (SD) manifestations, including shock, can happen during primary infection (PI) too and the mechanisms involved are less understood. To characterize the severe manifestations associated to PI, we distinguished between primary and secondary dengue cases in hospitalized patients from a region of low and recent dengue incidence in central Mexico. This region can serve as a model for dengue's behavior as it spreads to new areas worldwide.

Methods: Dengue-specific immunoglobulin M (IgM) and IgG concentrations were measured in the serum of 78 hospitalized patients with dengue hemorrhagic fever, and their ratios were used to discriminate between PI and SI, as recommended by World Health Organization. Clinical and laboratory manifestations were compared between PI and SI.

Results and Conclusions: PI was detected in 23% of hospitalized dengue cases, a proportion similar to that reported in high-incidence regions in Mexico. PI was more frequent in 16- to 40-year-olds, and was absent in patients older than 60 years. Only dengue with warning signs and SD were present in the studied population of hospitalized patients, and case frequency decreased with clinical severity both in PI and SI groups. No significant differences in demographics, laboratory tests, or symptoms were found between PI and SI, which illustrates that cases requiring hospitalization during outbreaks can be severe, even if they are PI. This information can help plan for sanitary contingencies in places where dengue is recently emergent and numerous PI cases are expected. The mechanisms involved in PI clinical severity need to be studied further.

Keywords: dengue primary infection, dengue outbreak, dengue IgG and IgM

Introduction

DENGUE IS A COMMON infection worldwide, with 4.0 billion people (half the world's population) currently at risk (Brady et al. 2012). It is caused by dengue virus (DENV),

an arbovirus (arthropod-borne virus) with four serotypes (DENV-1 to 4) that circulate periodically (Wash et al. 2015). Because of its recent and rapid spread all over the world, DENV is considered an emerging pathogen and it is endemic in at least 128 countries (Brady et al.

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2012). Nearly 60 million symptomatic dengue infections occur each year, resulting in ~10,000 deaths (Stanaway et al. 2016).

To aid clinical decisions, the World Health Organization (WHO) issued guidelines for the classification of dengue manifestations in 1997 and 2009 (WHO 1997, 2009a). The 1997 classification grouped symptomatic cases into three categories: undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF). DHF was further classified into severity grades (I–IV), with the last two grades defined as dengue shock syndrome (DSS) (WHO 1997). Because many clinically severe cases did not qualify as DHF, new guidelines were issued in 2009, now grouping cases into dengue without warning signs, dengue with warning signs (DWWS), and severe dengue (SD) that includes DSS (WHO 2009a). The advantages of the new classification have been discussed (Abello et al. 2016, da Silva et al. 2018); however, the 1997 classification remains in use among some clinicians and in literature.

A secondary infection (SI) with a different DENV serotype (heterotypical infection) has been recognized as a contributor to severity, related to the phenomenon of antibody-dependent infection enhancement. In this immunopathological phenomenon immunoglobulin G (IgG) immune complexes mediate the worsening of dengue by favoring viral replication, with the consequent release of proinflammatory cytokines and chemokines that increase vascular permeability and can lead to shock (Halstead 2014). However, severe clinical manifestations, including DSS, have also been reported during primary infection (PI) with some DENV serotypes (Soo et al. 2016) and the mechanisms involved in severity remain poorly understood. The relative risk of SD in SI versus PI has been estimated as ranging from 2 to 7 (Halstead and Wilder-Smith 2019).

PI and SI can be discriminated by analyzing dengue-specific immunoglobulins during the acute phase of the infection (first 8 days of symptoms). In PI, IgM is the first isotype to appear, detectable in 50% of patients by day 3 and in 80% by day 5 after symptom onset, followed by IgG detectable at low levels around day 10 (WHO 2009b, Halstead and Wilder-Smith 2019). In SI, IgG is the dominant isotype present at high levels from symptom start, with low or undetectable IgM levels during the acute phase (WHO 2009b).

In the last 10 years, the four DENV serotypes have circulated in Mexico. Similar to other world regions, DENV has rapidly spread to nonendemic regions of the country (Dantés et al. 2014) and DHF has increased (Dantés et al. 2014, SSA 2016), especially in the young, including children (Dantés et al. 2014, Torres-Galicia et al. 2014).

Disease severity during PI has not been evaluated in regions of low DENV incidence where this pathogen is emergent. These regions could present numerous PI cases during outbreaks, as most population has not been exposed to DENV. Characterization of PI severity in this scenario can aid the planning for dengue-related sanitary emergencies in regions of recent dengue spread, which are predicted to increase because of population dynamics and climate change. For this reason, we studied the proportion of dengue PI and SI and compared their clinical manifestations in hospitalized patients in a region of recent and low dengue incidence in central Mexico.

Materials and Methods

Ethical statement

This research was approved by the Local Committee of Ethics and Health Research of the Instituto Mexicano del Seguro Social (IMSS); registry numbers R-2011-2103-24, R-2011-2103-29 and of the Benemérita Universidad Autónoma de Puebla, registry number 100336999-VIEP-BUAP2018.

Patients and location

We conducted a retrospective study that included all the patients with confirmed dengue that required hospitalization in the General Hospital of Zone No. 5 (HGZ5), IMSS, during the dengue outbreak between June 11 and December 15, 2015 (6 months). Patients were referred from primary care with dengue symptoms and marked thrombocytopenia and neutropenia to the concentration hospital mentioned previously. This hospital is a public health care institution located in Metepec, Atlixco, Puebla, that serves the majority of the population of the Atlixco-Izucar de Matamoros Valley (18°54'31" N 98°27'55" W). The region is located at an altitude 1282–1834 meters above sea level (masl) and includes two cities: Atlixco (132,827 inhabitants) and Izucar de Matamoros (41,042 inhabitants) and the agricultural valley between/around them (INEGI 2017).

Dengue diagnosis

DENV infection was confirmed upon hospitalization in all patients, by qualitative identification of DENV-specific antibodies using Dengue Duo IgM and IgG Capture enzyme-linked immunosorbent assay (ELISA) (PanBio Pty Ltd., Brisbane, Australia) and by the detection of the nonstructural protein 1 (NS1) antigen of DENV (Platelia, Bio-Rad, Hercules, CA) in sera.

Clinical data

Blood samples were processed in the hospital's certified clinical laboratory, in a Cell-Dyn Emerald Hematology Analyzer (Abbott Laboratories, IL) for blood biometrics and in a Dimension RxL Max Integrated Chemistry System (Siemens Healthcare GmbH, Erlangen, Germany) for blood chemistry, liver function tests, and electrolytes. Abdominal ultrasound and other tests were carried out according to standard hospital procedures.

Quantitative determination of dengue IgG and IgM in sera and criteria for discrimination of PI versus SI

To discriminate between PI and SI, DENV-specific IgG and IgM were quantified with commercial ELISA kits (DRG International, Inc., Springfield, NJ) in sera samples obtained at hospital admission and stored at –80°C until use. Patients who had positive IgM and negative IgG were classified as PI, whereas patients with negative IgM and positive IgG were classified as SI. In patients with positive IgM and positive IgG, we used a ratio of IgM/IgG ≥ 1.2 for PI and IgM/IgG < 1.2 for SI, at 1:100 sera dilution, as suggested by the WHO (2009b).

TABLE 1. DEMOGRAPHICS AND DIAGNOSTIC DATA OF DENGUE HEMORRHAGIC FEVER IN 78 HOSPITALIZED PATIENTS FROM THE VALLEY OF ATLIXCO-IZUCAR DE MATAMOROS, PUEBLA, MEXICO

	n (% of total) ^a	p
Gender		
Female/male	41 (52.6)/37 (47.4)	1.000
Average age in years (95% CI)	39.6 (35.2–44.0)	
Groups by age and gender F/M		
7–15	7 (9.0)/5 (6.4)	
16–40	15 (19.2)/16 (20.5)	
41–60	12 (15.4)/11 (14.1)	0.906
>60	7 (9.0)/5 (6.4)	
Patients admitted during the early or late acute phase ^b		
Early (1–4 days)	52 (66.6)	<0.01
Late (5–8 days)	26 (33.4)	
Average days from symptom onset to admission (95% CI)	4.0 (3.8–4.4)	
Cases classified according to 1997 Dengue guidelines		
DHF-I	40 (51.2)	
DHF-II	24 (30.8)	<0.01
DHF-III	14 (18.0)	
DHF-IV	0 (0.0)	
Total	78 (100.0)	
Cases classified according to 2009 Dengue guidelines		
Dengue, without warning signs	0 (0.0)	
Dengue, with warning signs (DWWS)	67 (85.9)	<0.01
Severe dengue (SD)	11 (14.1)	
Total	78 (100)	

^aExcept when indicated otherwise, for example for the average age and average days from onset to admission.

^bThe acute phase includes days 1–8 after symptom onset.
CI, confidence interval; DHF, dengue hemorrhagic fever.

Statistical analysis

Frequencies, percentages, averages, confidence intervals, Student's *t*, chi-squared and Fisher's exact tests were calculated in IBM SPSS Statistics V21.0 (IBM Corp., Armonk, NY). Significant differences were considered at $p < 0.05$.

Dengue classifications

DHF grades I and II were infections without signs of shock, grade III was impending shock, and grade IV was profound shock, as stated in the WHO 1997 dengue guidelines (WHO 1997). DWWS and SD were defined according to WHO (2009a).

Results

We studied PI versus SI during the 2015 dengue outbreak in the valley of Atlixco-Izucar, Mexico. At admission, patients were classified according to WHO (1997) as that classification was in use at the studied hospital. All patients had DHF: 51.2% classified as DHF-I, 30.8% as DHF-II, 18% as DHF-III, and no patients had DHF-IV. For this study, we retrospectively reclassified patients according to the 2009 guidelines (WHO 2009a): 85.9% presented DWWS and 14.1% presented SD (Table 1).

We measured the dengue-specific immunoglobulin ratio during the acute phase, in the 78 DHF samples obtained at hospital admission. Most patients had IgM (–) and IgG (+) or IgM (+) and IgG (+) (Table 2). A total PI of 23% (95% confidence interval [CI] = 14–32) was found in the

studied population: 1 patient (1.3%) qualified as PI because he presented only IgM with no IgG, whereas the other 17 patients (21.7%) qualified using the IgM/IgG ratio ≥ 1.2 (Table 2). Regarding SI, 19 patients (24.4%) were detected with the IgM/IgG ratio < 1.2 , and other 41 (52.6%) with IgM (–)/IgG (+), for a total SI of 77% (Table 2). The frequency of dengue-specific IgG levels $\geq$ average was the same in PI and SI patients. IgM was detected significantly more in PI (Table 2).

PI was more frequent in 16- to 40-year-olds (61.1%), and it was absent in patients ≥ 60 years (Table 3). DHF-I predominated in both PI and SI groups, whereas DHF-III was the least frequent severity grade in both groups (Table 3). When reclassified by the 2009 guidelines, 83.3% of patients with PI presented DWWS, similar to 86.7% of patients with SI (Table 3). Among PI patients, 55.5% were admitted during the late acute phase versus 26.7% of patients with SI (Table 3). No significant differences in symptoms, hematological or biochemical data were detected between patients with PI or SI (Table 4).

Discussion

Since 1978, dengue has been endemic in the tropical and subtropical areas of Mexico, but incidence has remained low in central Mexico. This is because climate/altitude limit the spread of dengue vectors to the most densely populated Mexican cities in central Mexico (located at >2000 /masl), despite being surrounded by endemic areas (Dantés et al. 2014). We studied dengue in the valley of Atlixco-Izucar, located in the state of Puebla in central Mexico (~ 1500 /masl). With a dry tropical climate most of the year and

TABLE 2. DENGUE-SPECIFIC IMMUNOGLOBULIN PROFILES USED FOR THE CLASSIFICATION OF PRIMARY AND SECONDARY DENGUE INFECTION IN HOSPITALIZED PATIENTS WITH DENGUE FROM THE VALLEY OF ATLIXCO-IZUCAR DE MATAMOROS, PUEBLA, MEXICO

Antigen or antibody detected and method	n patients (% of total) ^a	p
Profiles detected through qualitative determination of dengue NS1, IgM and IgG		
NS1(+), IgM(−), IgG(−)	0 (0.0)	
NS1(+), IgM(+), IgG(−)	1 (1.3)	
NS1(+), IgM(+), IgG(+)	36 (46.1)	
NS1(+), IgM(−), IgG(+)	41 (52.6)	
Total	78 (100)	
Profiles detected through quantitative determination of dengue IgG and IgM		
IgM(+), IgG(+)	36 (46.1)	
IgM (+), IgG(−)	0 (0.0)	
IgM(−), IgG(+)	42 (53.9)	
Total	78 (100.0)	
Dengue IgM and IgG levels, average (95% CI)		
IgG	19.9 (19.4–20.3) DU	
IgM	26.3 (22.0–30.3) DU	
Profiles of patients classified as primary infection		
IgM/IgG ≥ 1.2	17 (21.7)	
IgM(+) ^b , IgG(−)	1 (1.3)	
Total PI	18 (23.0) (95% CI 14–32)	
Profiles of patients classified as secondary infection		
IgM/IgG <1.2	19 (24.4)	
IgM(−), IgG(+)	41 (52.6)	
Total SI	60 (77.0) (95% CI 69.7–86.3)	
Patients with dengue IgG ≥ 19.9 DU ^c		
Primary infection	12 (66.6% of PI)	0.916
Secondary infection	38 (63.3% of SI)	
Patients with detected dengue IgM		
Primary infection	17 (94.4% of PI)	<0.001
Secondary infection	19 (31.7% of SI)	

Dengue specific immunoglobulin levels were detected quantitatively above the following values: IgG > 10 DU, IgM > 11 DU (minimal detection levels).

DU, detection units = patients' (mean) absorbance value $\times 10/\text{CO}$ (control cut-off).

^aExcept when indicated otherwise.

^bIn this patient, dengue IgM was detected qualitatively.

^cCorresponds to dengue IgG $\geq$ the average for this population of hospitalized dengue patients.

IgG, immunoglobulin G; IgM, immunoglobulin M; PI, primary infection; SI, secondary infection.

limited by highlands, this valley represents a transition zone between places of low and high dengue incidence. According to the Mexican Ministry of Health, during 2015–2016, the state of Puebla had an incidence of 0.01–13.1 dengue cases per 100,000 inhabitants, although it borders the states of Morelos and Guerrero, which have much higher incidences, ranging from 26.2 to 39.3 cases per 100,000 (SSA 2016).

There have been three recent and well-documented dengue outbreaks in the Atlixco-Izucar Valley: 2009–2010, when serotype DENV-1 prevailed (Vázquez-Pichardo et al. 2011); 2012–2013 dominated by DENV-2 (SSA 2014); and 2015 when DENV-1 was again more frequent, and DENV-4 was reported for the first time in the region (SSA 2016). Here we analyzed the rate of PI in 78 patients with dengue that required hospitalization during the last documented outbreak in the region. We included all the patients with confirmed dengue, admitted during the entire outbreak to the concentration hospital that serves most of the population of the Valley. The number of patients was only limited by the low dengue incidence in the region.

We used the recommendation to discriminate PI from SI with an IgM/IgG ratio > 1.2 (WHO 2009b) in samples obtained in the acute phase (at hospital admission). With this strategy, we found 23% (95% CI = 14–32) PI in the studied population of hospitalized patients (Table 2). This is similar to the PI of 29.8% (95% CI = 18.8–40.8) reported previously in DHF patients from a Mexican region long endemic and with high DENV incidence (state of Veracruz, 26.18–39.23 dengue cases/100,000 inhabitants in 2015–2016) (SSA 2016). It should be noted, however, that the PI rate that we calculated does not reflect overall PI as we studied only dengue cases that required hospitalization. The rate of PI considering all dengue cases has been scarcely reported for Mexico (Posadas-Mondragón et al. 2017); and a different study design would be needed to compare overall PI in low-versus high-incidence Mexican regions.

PI in other world regions has been reported at 31% and 29% in Brazilian patients with DHF or DF/DHF (Guilarde et al. 2008), and at 44.7% in Sri Lankan children (Bodinayake et al. 2018), whereas meta-analyses have calculated 36.6% of PI in DHF for Southeast Asia and 10.6% for Latin America

TABLE 3. DEMOGRAPHICS AND DENGUE CLASSIFICATION OF HOSPITALIZED PATIENTS WITH PRIMARY VERSUS SECONDARY DENGUE INFECTION FROM THE VALLEY OF ATLIXCO-IZUCAR DE MATAMOROS, PUEBLA, MEXICO

	PI	SI	p
Gender, <i>n</i> (% of group)			
Female	12 (66.6)	29 (48.8)	0.191
Male	6 (34.4)	31 (52.2)	
Total	18 (100.0)	60 (100.0)	
Age in years			
Range	7–60	8–89	0.191
Average (95% CI)	34.3 (26.6–42.0)	41.2 (35.9–46.5)	
Groups by age, <i>n</i> (% of group)			
7–15	3 (16.7)	9 (15.0)	1.00
16–40	11 (61.1)	20 (33.3)	0.033
41–60	4 (22.2)	19 (31.7)	0.561
>60	0 (0.0)	12 (20.0)	0.048
Total	18 (100.0)	60 (100.0)	
Patients admitted during the early or late acute phase, <i>n</i> (% of group)			
Early (1–4 days)	8 (44.5)	44 (73.3)	0.043
Late (5–8 days)	10 (55.5)	16 (26.7)	
Total	18 (100.0)	60 (100.0)	
Average days from symptom onset to admission (95% CI)	4.0 (3.3–4.8)	3.8 (3.5–4.3)	0.658
Cases classified according to 1997 Dengue guidelines, <i>n</i> (% of group)			
DHF-I	11 (61.2)	29 (48.3)	0.424
DHF-II	4 (22.2)	20 (33.3)	0.561
DHF-III	3 (16.6)	11 (18.4)	1.00
DHF-IV	0 (0.00)	0 (0.00)	—
Total	18 (100.0)	60 (100.0)	
Cases classified according to 2009 Dengue guidelines, <i>n</i> (% of group)			
Without warning signs	0 (0.00)	0 (0.00)	—
With warning signs	15 (83.3)	52 (86.7)	0.709
Severe dengue	3 (16.7)	8 (13.3)	
Total	18 (100.0)	60 (100.0)	

(Soo et al. 2016). The low PI suggested for Latin America needs confirmation with more studies. In a retrospective study that analyzed 30 years of fatal dengue cases in Brazil, deaths were observed significantly more in PI than in SI (Guerra-Nunes et al. 2018), supporting that PI can be severe.

Despite the recent dengue spread to the Atlixco-Izucar Valley, most of the patients requiring hospitalization during this outbreak had a previous dengue infection (77% SI), possibly from previous outbreaks in the region. This behavior was expected as SI entails a higher risk of severity than PI (Halstead and Wilder-Smith 2019).

Overall, case frequency decreased with disease severity, but the distribution of cases throughout the severity spectrum was not different between PI and SI with either of the two WHO classifications (Table 3). This is compatible with results from Thailand where PI and SI were similar between DHF-I and DHF-II (Wichmann et al. 2004). In addition, we found a good agreement in case classification with the 1997 and 2009 WHO guidelines, similar to a recent report (da Silva et al. 2018).

Our study detected more PI in the young, in general agreement with studies in other countries, where PI has been detected more frequently in children than in adults (Bodinayake et al. 2018). However, the most frequent age range for PI in our study (16–40 years) corresponds to productive age. This is likely related to: (i) the low incidence in the region and (ii) the opportunity of exposition to the vector: the Atlixco-Izucar Valley is an agricultural region where workers are

exposed to mosquitoes in the fields. An important advantage of studying severe PI in a low-incidence region is that PI can be found at diverse ages, whereas in high-incidence regions PI is almost limited to children.

The average number of days from symptom onset to hospital admission was not different between PI and SI groups (Table 3). Thus, samples used to discriminate between PI and SI were obtained equally early during the acute phase. Half the PI patients were hospitalized in the late acute phase (5–8 days after onset) versus only a quarter of SI patients (Table 3). This could reflect that PI patients took slightly longer to seek medical attention, because they were not familiar with dengue symptoms. Alternatively, there could be an underestimation of PI among patients evaluated in the early acute phase: because we did not evaluate the progression of the immunoglobulin profile, we cannot rule out that a minority of patients evaluated very early in the acute phase had higher IgM levels a few days later. However, the presence of IgG in these patients early in the acute phase strongly suggests SI; thus, the underestimation of PI in this group is unlikely.

Exanthema, epistaxis, and gingival bleeding tended to be more frequent in SI patients (Table 4), whereas plasma leakage and petechiae were observed at similar percentages in PI and SI (Table 4), and ascites and mottled skin were not present in PI (Table 4).

Using published criteria for clinical assessment (Tomashak et al. 2018), 27.7% of our patients with PI qualified as

TABLE 4. CLINICAL AND LABORATORY PARAMETERS OF HOSPITALIZED PATIENTS WITH PRIMARY VERSUS SECONDARY DENGUE FROM THE VALLEY OF ATLIXCO-IZUCAR DE MATAMOROS, PUEBLA, MÉXICO

	Primary infection	Secondary infection	p	Normal values
Laboratory parameters, average (95% CI)				
Temperature (°C)	38.8 (38.3–39.3)	38.9 (38.7–39.3)	0.562	37°C
% Hematocrit for age 7–15 years	45.4 (33.2–57.5)	45.3 (40.8–49.7)	0.980	40 ^a
% Hematocrit, females	42.8 (38.8–45.9)	43 (41.5–44.5)	0.893	42.4 ^b (41.2–43.4)
% Hematocrit, males	48 (45–50)	49.2 (47.3–51)	0.587	47.3 ^b (45.7–48.8)
Platelets, 10 ³ /μL	40.1 (25.6–54.6)	30 (25.2–36.1)	0.215	150–400
Leukocytes, 10 ³ /μL	4.0 (3.4–4.8)	4.3 (3.9–4.7)	0.505	4.2–10.8
Lymphocytes, 10 ³ /μL	1.3 (0.94–1.70)	1.5 (1.29–1.70)	0.419	1.2–3.8
Neutrophils, 10 ³ /μL	2.45 (1.75–3.15)	2.64 (2.11–3.16)	0.719	1.8–7.0
ALT in IU/L	126 (83–168)	98 (77–119)	0.191	16–63
AST in IU/L	177 (112–243)	133 (108–158)	0.194	15–37
Albumin in g/dL	3.1 (2.9–3.3)	2.9 (2.7–3.0)	0.060	3.4–5.0
Calcium in mg/dL	7.7 (7.6–7.9)	7.9 (7.7–8.0)	0.290	8.5–10.1
Symptoms/signs, n (% of group)				
Fever, cephalgia, arthralgia, retroocular pain, myalgia	18 (100)	60 (100)	1.00	—
Trombocytopenia	6 (33.3)	20 (33.3)	0.684	>5.0–10 × 10 ⁴ /μL
Moderate trombocytopenia ^c	7 (38.9)	29 (48.3)		2.0–5.0 × 10 ⁴ /μL
Severe trombocytopenia ^c	5 (27.8)	11 (18.4)		<2.0 × 10 ⁴ /μL
Total	18 (100)	60 (100)		
Hypoalbuminemia	17 (94.4)	57 (95)	1.00	<3.4 g/dL
Hypocalcemia	18 (100)	57 (95)	1.00	<8.0 mg/dL
Exantema	1 (5.6)	12 (20)	0.278	
Plasma leakage	12 (66.7)	31 (51.6)	0.292	
Petechiae	10 (55.5)	30 (50)	0.790	
Ecchymosis	2 (11.1)	3 (5.0)	0.325	
Ascites	0 (0.0)	2 (3.3)	1.00	
Mottled skin	0 (0.0)	2 (3.3)	1.00	
Gingival bleeding	2 (11.1)	15 (25)	0.213	
Epistaxis	2 (11.1)	16 (26.7)	0.216	
Hematemesis	1 (5.5)	5 (8.3)	0.658	
Melena/blood in stool	1 (5.5)	3 (5.0)	1.00	

^aNormal hematocrit value at altitude 2,200/masl (López-Santiago 2016).

^bNormal hematocrit values at altitude 970–1923/masl (Trompetero-González et al. 2015).

^cAccording to Tomashek et al. (2018).

ALT, alanine transaminase; AST, aspartate transaminase; masl, meters above sea level.

severe thrombocytopenia and 38.8% had moderate thrombocytopenia, without significant differences compared with SI (Table 4). We observed a decrease in albumin, along with elevated alanine transaminase (ALT) and aspartate transaminase (AST) in both PI and SI (Table 4) denoting liver inflammation, which has been associated with severity (Oliveira et al. 2016, Posadas-Mondragón et al. 2017); however, there were no cases of acute hepatitis marked by >10 times ALT increase, unlike in other studies (Souza et al. 2004). It has been reported that Ca²⁺ levels correlate with disease severity, with hypocalcemia being more prevalent in DHF than in DF (Constantine et al. 2014). Our results agree with that report, although hypocalcemia was found at a similar percentage in PI and SI (Table 4).

All studied patients had hydration management at primary care before referral. This likely explains the near-normal hematocrit values observed in our patients. However, hematocrit was higher at admission than at discharge (Supplementary Fig. S1) and hematocrit in patients aged 7–15 years increased 12.5% above normal for the age (Table 4), similar to another study (Bodinayake et al. 2018).

A limitation of our study is that the DENV serotype was not determined, thus we cannot discard that a particular serotype was associated with severity in either PI or SI. We know that serotypes DENV-1 and DENV-2 have predominated alternately in the three recent dengue outbreaks in the Atlixco-Izucar Valley with DENV-1 predominating and DENV-4 reported for the first time in the outbreak studied here (SSA 2016).

Conclusions

In this study PI was detected in 23% of patients requiring hospitalization in a Mexican region of low and recent DENV incidence. These results provide evidence that PI dengue can include DHF-II and III or SD cases, during outbreaks, which increases the burden to health systems. More studies to determine the proportion and characterize the severity of PI dengue and its related mechanisms are needed in Latin America and worldwide.

Author Disclosure Statement

No conflicting financial interests exist.

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Supplementary Material

Supplementary Figure S1

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