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Clinical markers associated with acute laboratory-confirmed *Dengue* infection: results of a national epidemiological surveillance system

Marcadores clínicos asociados con la infección de *Dengue* confirmada por laboratorio: resultados del sistema nacional de vigilancia epidemiológica

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ABSTRACT

Objective To evaluate the association of several clinical markers with acute laboratory-positive *Dengue* Virus infection.
Methods A hospital-based case-control study was conducted in the state of Colima, Mexico, by using information from the National System of Epidemiological Surveillance (Sistema Nacional de Vigilancia Epidemiológica [SINAVE]) for Dengue. Data from 2 732 cases and 2 775 frequency-matched controls were analyzed. Odds Ratio (OR) and the 95 % Confidence Interval (CI), estimated by means of logistic regression models, were used.
Results The presence of skin rash (OR=1,7; 95 % CI 1,5–2,1), persisting vomiting (OR=1,8; 95 % CI 1,5–2,3) and increased capillary fragility (petechiae, ecchymosis, hematoma or positive tourniquet test; OR=1,8; 95 % CI 1,2–2,6) were associated with laboratory-positive infection.
Conclusions Three clinical markers were significantly associated with an increased risk of acute laboratory-confirmed *dengue* infection. These findings would support accurate and timely diagnosis of *dengue* in laboratory-limited settings.

Key Words: Dengue; epidemiology; population surveillance; communicable diseases; case-control studies *(source: MeSH, NLM)*.

RESUMEN

Objetivo Evaluar la asociación de distintos marcadores clínicos con la infección por virus de Dengue, confirmada por laboratorio.
Métodos Se condujo un estudio hospitalario de casos y controles, en el estado de Colima, México, usando información del Sistema Nacional de Vigilancia Epidemiológica (SINAVE) para dengue. Se analizó la información de 2 732 casos y 2 775 controles de frecuencia compatible/pareada. Se utilizó la Razón de Momios (RM) y el Intervalo de Confianza de 95 % (IC), estimado con modelos de regresión logística.
Resultados La presencia de exantema (OR=1,7; 95 % CI 1,5–2,1), vómito persistente (OR=1,8; 95 % CI 1,5–2,3) y fragilidad capilar aumentada (petequias, equimosis, hematomas o prueba del torniquete positiva; OR=1,8; 95 % CI 1,2–2,6) se asociaron con la infección por *dengue* confirmada por laboratorio.
Conclusiones Tres marcadores clínicos se asociaron significante con un riesgo incrementado de la infección aguda por *dengue* confirmada por laboratorio. Estos hallazgos pueden apoyar al preciso y oportuno diagnóstico de la infección en sitios con acceso limitado a laboratorios.

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Palabras Clave: Dengue; epidemiología; vigilancia de la población; enfermedades transmisibles; estudios de casos y controles *(fuente; DeCS, BIREME)*.

Dengue is an epidemic disease transmitted to humans by the bite of infected mosquitoes (*Aedes aegypti* and *Aedes albopictus*) and it is caused by Dengue Virus (DENV) (1). Approximately 40 % of the population of the world is at risk of pathogen transmission (2). In Mexico, all DENV serotypes (DENV 1 - 4) have been isolated. Additionally, disease transmission in most of Mexican states has been reported (3).

Mexican health services are obligated to report suspected cases of *dengue* using a web-based platform from the National Epidemiological Surveillance System (SINAVE) (4,5). The 1997 World Health Organization (WHO) *dengue* case definition was used during 2014 and suspected cases were classified as *dengue* fever (DF), *dengue* hemorrhagic fever (DHF) or *dengue* shock syndrome (DSS) (6).

Timely diagnosis and supportive initial treatment reduce *dengue* mortality and may potentially prevent additional cases among contacts (7). Since the spectrum of clinical manifestations of *dengue* is wide, early diagnosis may be difficult to detect (8,9). This study aimed to evaluate the association of clinical markers with acute laboratory-positive *dengue infection* using data from large case-control study conducted in an endemic area.

MATERIALS AND METHODS

Study population

A hospital-based case-control study was conducted in the state of Colima, Mexico, by using data from the SINAVE. Incident cases (n=2 732) —included individuals aged from 3 years old and on— were reported, from January to December in 2014, as clinically suspected cases of *dengue* (fever≥2 of the following: headache, myalgia, arthralgia, retro-orbital pain or skin rash) that were subsequently and serologically confirmed as *dengue infection* cases. A multistage probabilistic sampling, according to age distribution of total confirmed cases from the database, was used in the selection of cases. *Dengue* serologic tests included ELISA (Enzyme-Linked Immunosorbent Assay), NS1 (nonstructural protein 1), and IgG/IgM (immunoglobulin G/M); and were performed by staff from the State Laboratory of Public Health in accordance with normative standards (4).

Controls (n=2775) —included subjects notified as suspected *dengue* cases with a subsequent negative serology test— were matched to the cases (frecuency-matching) according to sex, five years old age groups, membership to a health care institution, and health jurisdiction of residence. Controls were randomly selected from individuals fulfilling the eligibility criteria.

Data regarding the clinical manifestations of study subjects were collected and included the initial disease classification (suspected DF, DHF or DSS); fever (yes/no); headache (yes/no); myalgia (yes/no); arthralgia (yes/no); retro-ocular pain (yes/no); skin rash (yes/no); persisting vomiting (yes/no); abdominal pain or tenderness (yes/no); clinical fluid accumulation (ascites, edema or pleural effusion; yes/no); increased capillary fragility (petechiae, ecchymosis, hematoma or positive tourniquet test; yes/no) and mucosal bleeding (gingival bleeding, epistaxis, hematemesis or melena; yes/no). Results of serology tests were also extracted from the database.

This study was approved by the National Commission for Clinical Research.

Statistical analysis

Summary statistics were used to compare cases and controls. To determine statistical association between the clinical manifestations and *dengue*, odds ratios (OR) and 95 % confidence intervals (CI) were estimated by means of unconditional logistic regression models. All analyses were conducted using Stata SE 11.0 (StataCorp, College Station, TX) and significance level was set at 5 %.

RESULTS

Table 1 shows the study population characteristics for selected variables. The mean age of cases and controls was 27,8±18,0 and 26,9±17,8 years respectively, and this difference did not reach statistical significance. When compared with controls, cases were more likely to be classified at first healthcare contact as DHF/DSS patients requiring hospital admission. Cases also had a significant higher prevalence of retroocular pain (85,3 % vs. 83,0 %), skin rash (17,1 % vs. 9,1 %), persisting vomiting (15,3 % vs. 5,9 %), abdominal pain (14,3 % vs. 6,5 %), clinical fluid accumulation (2,4 % vs. 0,3 %), increased capillary fragility (9,1 % vs. 1,5 %) and mucosal bleeding (5,6 % vs. 1,3 %).

In multiple analyses (Table 2), clinical markers associated with laboratory-positive *dengue infection* were skin rash (OR=1,7; 95 % CI 1,5–2,1), persisting vomiting (OR=1,8; 95 % CI 1,5–2,3) and increased capillary fragility (OR=1,8; 95 % CI 1,2–2,6).

Table 1. Characteristics of participants by case control status

Variables	Cases		Controls		p[a]
	n=2 732	(%)	n=2 775	(%)	
Age (years)[b]	28,8 ± 17,7		28,2 ± 17,2		0,7
Sex					
Female	1 356	(49.6)	1 405	(50,6)	0,5
Days elapsed from fever onset to seek healthcare in a health center or hospital	4,6 ± 6,9		3,9 ± 3,3		0,2
Disease classification at first healthcare contact					
DF	1 859	(68,1)	2 605	(93,9)	< 0,001
DHF/DSS	873	(31,9)	170	(6,1)	
Hospital admission					
Yes	701	(25,7)	163	(5,9)	< 0,001
Headache					
Yes	2 688	(98,4)	2 727	(98,3)	0,7
Myalgia					
Yes	2 611	(95,6)	2 630	(94,8)	0,2
Arthralgia					
Yes	2 542	(93,0)	2 569	(92,6)	0,5
Retro-ocular pain					
Yes	2 330	(85,3)	2 303	(83,0)	0,02
Skin rash					
Yes	468	(17,1)	253	(9,1)	< 0,001
Persisting vomiting					
Yes	417	(15,3)	165	(5,9)	< 0,001
Abdominal pain					
Yes	390	(14,3)	181	(6,5)	< 0,001
Clinical fluid accumulation[c]					
Yes	66	(2,4)	9	(0,3)	< 0,001
Increased capillary fragility[d]					
Yes	250	(9,1)	41	(1,5)	< 0,001
Mucosal bleeding[e]					
Yes	4	(5,6)	36	(1,3)	< 0,001

Relative frequency is shown (%) unless otherwise specified. Abbreviations: DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; [a] From t-test or chi-square test as corresponding; [b] Arithmetic mean (standard deviation); [c] Ascites, edema or pleural effusion; [d] Petechiae, ecchymosis, hematoma or positive tourniquet test; [e] Gingival bleeding, epistaxis, hematuria, abnormal vaginal bleeding, hematemesis or melena.

Table 2. Bivariate and multiple analysis between clinical markers and laboratory-positive dengue infection

Variables		Bivariate analysis				Multiple analysis			
		OR[a]	95 % CI		p	OR[b]	95 % CI		p
Headache	No	1,0				1,0			
	Yes	1,1	0,7	1,8	0,6	1,1	0,7	1,7	0.7
Myalgia	No	1,0				1,0			
	Yes	1,1	0,8	1,4	0,7	1,1	0,8	1,5	0.6
Arthralgia	No	1,0				1,0			
	Yes	0,9	0,8	1,2	0,8	0,9	0,7	1,3	0.7
Retro-ocular pain	No	1,0				1,0			
	Yes	1,1	0,9	1,3	0,3	1,1	0,9	-1,3	0.5
Skin rash	No	1,0				1,0			
	Yes	1,8	1,5	2,2	< 0,001	1,7	1,5	2,1	< 0.001
Persisting vomiting	No	1,0				1,0			
	Yes	2,0	1,7	2.5	< 0,001	1,8	1,5	2,3	< 0.001
Abdominal pain	No	1,0				1,0			
	Yes	1,6	1,3	2,0	< 0,001	1,3	1,0	1,6	0.1
Clinical fluid accumulation[c]	No	1,0				1,0			
	Yes	1,6	0,8	3,4	0,2	1,2	0,6	2,6	0,6
Increased capillary fragility[d]	No	1,0				1,0			
	Yes	2,2	1,5	3,2	< 0,001	1,8	1,2	2,6	0,003
Mucosal bleeding[e]	No	1,0				1,0			
	Yes	1,3	0,9	1,9	0,2	1,0	0,7	1,6	0,8

[a] Odds ratios adjusted (by design) by sex, 5-year age groups, membership to a health care institution and health jurisdiction of residence. [b] Odds ratios adjusted by sex, 5-year age groups, membership to a healthcare institution and health jurisdiction of residence, disease classification at first contact with healthcare and by the variables presented in the table. [c] Ascites, edema or pleural effusion. [d] Petechiae, ecchymosis, hematoma or positive tourniquet test. [e] Gingival bleeding, epistaxis, hematuria, abnormal vaginal bleeding, hematemesis or melena. [a,b] Unconditional logistic models were used.

DISCUSSION

We found that three clinical markers were associated with laboratory-confirmed *dengue virus infection*: skin rash, persisting vomiting and increased capillary fragility. *Acute dengue* illness is characterized by nonspecific signs and symptoms that are difficult to distinguish from other febrile illnesses (10). Moreover, in laboratory limited health care settings, a diagnostic algorithm based on clinical markers could improve early medical management and disease outcomes.

Previously published studies have described variations in clinical *dengue* features between them (11,12). Differences may be secondary to host response to infection (13).

Headache and retro-ocular pain are grouped in the WHO 2009 *dengue* case definition (14). The association of headache and retro-ocular pain with confirmed disease was not significant when they were analyzed combined (OR=1,6; 95 % CI 0,8–3,2; data not presented), which is consistent with a previously published study (15). *Dengue*-related ocular manifestations have been described in 10–40 % of confirmed cases (16,17).

Hospital admission rate was 25,7 % and 5,9 % in cases and controls respectively. This finding is lower to rates reported in other American or Asian populations (45 % - 80 %) (18,19). DENV-2 was the most frequent serotype isolated (87,8 %) and it has been associated with increased risk of developing DHF or DSS (20). In the study sample, 68,1 % and 31,9 % of cases were classified as DF and DHF as corresponding; no DSS cases were registered.

The autochthonous transmission of chikungunya virus and zika virus was first observed in Mexico on 2014 and 2015 respectively (21,22). There are clinical characteristics that may be helpful to distinguish between acute cases of *dengue*, chikungunya or zika infection in limited health-care settings (23,24).

There are some limitations in this study. First, cases and controls were selected from health services users and might not reflect the whole dengue-infected group. However, our results are useful in health care settings from dengue endemic areas. Second, data regarding *dengue* all warning signs —included in the 2009 WHO case definition— were not collected systematically by the analyzed surveillance system. In Mexico, the 1997 WHO case definition is used for epidemiological purposes. Third, this study was conducted in a population with high incidence of *dengue infection*, which means our findings may not be reproducible in a non-endemic area.

The results of this study suggest that clinical data may be used to identify *acute dengue infection*. To our knowledge, this is the first evaluation of interactions between age and clinical markers; further research is needed to understand better our findings ◆

Conflict of interest: None.

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