Neurological Presentation of Severe Dengue in Children From a Colombian Hyperendemic Area

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Research note

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Abstract

Objective: Dengue transmission is sustained in Colombia with increasing prevalence mainly in children. This work was aimed to describe a cases series of children diagnosed with dengue presenting neurological disease in the Huila province of Colombia. Eleven pediatric febrile patients confirmed to dengue disease and presenting neurological signs were studied in the University Hospital of Neiva, Huila province. Clinical and laboratory findings, CSF cytochemical analysis, neurology images, and serology and molecular studies were performed.

Results. Viral RNA was detected in all patients' sera by RT-PCR. Nine out of 11 were primary infections. Tonic-clonic seizures (73%), consciousness alterations (27%), irritability (27%) and ataxia (18%) were the most frequent neurological signs. None of the patients had plasma leakage, hypovolemic shock or liver disease, confirming the encephalitis diagnosis. Diagnostic images did not show abnormal findings neither bacterial or fungal infections were detected in CSF analysis. All patients survived without sequelae except in one patient that presented ataxia for months. In conclusion, we described a group of children with neurological signs during severe dengue disease as the main finding, indicating the importance of include dengue as a differential diagnosis in neurological patients from endemic areas.

Introduction

The world estimate of dengue infections is around 390 million people among symptomatic and asymptomatic cases in endemic countries such those of Latin America, Asia southeast and Pacific islands [1]. Near the 65% of Colombian municipalities reported constant *Aedes* infestation [2] and dengue incidence increase year after year mainly associated with abnormal environmental sanitary conditions, broad circulation of the four serotypes and high mosquito infestation [3, 4]. In America, most of the cases occur in individuals under 15 years of age [5]. The current disease classification proposes to identify dengue following the clinical signs and symptoms to establish the most accurate diagnostic and recognize early those cases could become severe or fatal [6]. Accordingly, dengue warning signs reflecting endothelial dysfunction should be revised are abdominal tenderness, vomit, edema, mucosal bleeding, hepatomegaly, irritability, or hypotension. In those presumptive dengue cases occurring with plasma leakage signs (pleural effusion, pericarditis) or respiratory distress, severe bleeding, or affectation of organs such as liver, brain or kidney, a diagnostic of severe dengue should be corroborated [7].

Even though neurological manifestations were reported since 1976 in Thailand as "dengue-associated acute encephalopathy" [8], from these years until today the incidence of neurologic manifestations during dengue disease have increased considerably [9]. Similar cases have been reported from the Asian Southeast and Pacific Islands to America [10, 11]. Today some hypothesis propose DENV could also be neurotropic as other flaviviruses supported by the frequent finding of specific IgM or viral RNA in cerebrospinal fluid (CSF) [12, 13] that could confirm CNS infection and direct brain injury. This finding allows the differentiation from those circulating virus and antibodies that could enter to CNS due to impairment of blood-brain barrier (BBB).

Many kinds of pathologies have been reported, from cerebral edema and hemorrhages to perivascular lymphocyte infiltrates and demyelination foci. These anomalies could be explained by i) BBB alteration induced by TNF-alpha and IL-6 activity involved in endothelial junction disruption favoring the virus entry to CNS, ii) DENV infection to endothelial cells leading to virion pass through to brain parenchyma [14, 15], and iii) endothelial cell injury by glycocalyx remodeling induced by NS1. Nervous system DENV replication has been observed in the olivary nucleus and cerebellum as well as tissue macrophages DENV positive indicating some neurotropism [16].

It has been reported that 47% of adult meningitis and encephalitis cases in a Brazilian endemic area were explained by acute DENV infection occurring during the first week of fever onset [17]. During that outbreak, the disorder does appear as encephalitis with behavioral disorders, seizures, and paresis with no evidence of liver failure and confirming serum or CSF IgM serology or altered neuroimages showing brain changes. Other cases with unspecific neurological signs could appear as consequence of metabolic alterations or prolonged shock, brain hypoxia, cerebral edema or liver or kidney failure, that explain the headache, retro-orbital pain, insomnia, restless and mood changes appearing in patients [18]. The Colombian study reported by Mendez and Gonzalez [19] described 46 out of 168 severe dengue children patients presenting encephalopathy and 3 with encephalitis diagnostic. Dengue encephalitis is considered when febrile patients in endemic areas, having one of these signs or symptoms headache, seizures, consciousness alterations and behavioral changes with no hepatic failure or bleeding and positive for DENV serology or molecular test in serum or CSF with altered brain images in tomography or resonance.

Objective

The purpose of this article is to present and describe the clinical, laboratory and diagnostic characteristics of eleven children diagnosed as dengue cases which presented neurological manifestations, cases occurring during regular endemic circulation in the Colombian province of Huila in the 2011 year.

Methods

Study design

This work was a descriptive retrospective study based on the review of the clinical characteristics of eleven dengue diagnosed children which had any neurological manifestation admitted to University Hospital Hernando Moncaleano Perdomo of Neiva city in the Huila province during the year 2011.

Data Collection

The University Hospital Hernando Moncaleano is the largest health setting in Neiva, the capital city of the Huila province located at 42 meters above the sea level with a mean temperature of 28 °C where it has been reported frequently dengue outbreaks. The Hospital Institutional Review Board approved the study

and parents, or guardians signed the consent form during the stay. We collected the clinical and laboratory information of those febrile patients with one of dengue symptoms such as rash, headache, retro-orbital pain, myalgia, arthralgia associated with any neurological signs like seizures, abnormal movements, acute flaccid palsy, lethargy, meningeal signs or consciousness alteration with no shock evidence, which were diagnosed as severe dengue following the recommendation of WHO. Clinical records from pediatric emergency department were revised from March to October 2011 and those patients with neurological signs and another microorganism associated were excluded.

One specific designed clinical report form was filled for each case and complete information of laboratory tests (blood cell counts, coagulation tests, liver, and kidney function markers), diagnostic images (tomography and chest Rx) and CSF chemical and microbiological analysis were collected. The enrolled cases were investigated for serum IgM and capture IgG by ELISA and for viral RNA detection by RT-PCR following the protocol described previously [20].

Results

During the study period, 34 patients with fever and neurological manifestations were examined but three were excluded (one by mental retardation and two by psychiatric disorder), the remaining 31 patients were investigated for dengue by serology or RT-PCR and eleven (35.5%) tested positive for any of them (two girls, nine boys). All of them, finally were discharged with severe dengue diagnostic or viral encephalitis, despite all them had positive dengue IgM or IgG test in serum. All but one patient had laboratory analysis, although this one had serology and RT-PCR results. Most of the patients (73%) presented seizure disorder or convulsions. In Table 1, complete data of patients are shown. Although all the patients were IgM positive, only two were IgG positive (secondary infection). All the sera were positive for RT-PCR for DENV, but only three of them allowed serotyping (DENV-1).

Table 1
Clinical and Laboratory findings of evaluated patients

Code	Age	Clinical Findings	Laboratory Findings	Images	Presumptive diagnosis	Dengue IgM	Dengue IgG	Cerebrospinal fluid analysis	Virology Test
430	8 months	Tonic-clonic seizure, fever, rash, hepatomegaly	Lymphocytic leukocytosis, Anemia, Thrombocytopenia	Simple and contrasted brain CAT scan with no lesion or midline alteration	Dengue with warning signs, febrile convulsions	Positive	Negative	Clear liquid, with no RBC or leukocytes. Glucose (59 mg/dL), Proteins (21.5 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+)
836	11 months	Four limbs hypotonic, epigastralgia, painful right hypochondrium, neck adenomegaly, fever	Leukocytosis, anemia, blood clotting alteration	Simple brain CAT scan with no lesions or hemorrhages	Febrile syndrome	Positive	Negative	Not available	RT-PCR (+)
148	12 months	Fever, tonic-clonic seizures, peri buccal cyanosis, mydriasis, tachypnea	Anemia	Simple brain CAT scan normal. Normal Chest radiography	Convulsive syndrome Meningitis	Positive	Negative	Clear liquid, with no RBC or leukocytes. Glucose (63 mg/dL), Proteins (22.1 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+) DENV-1
273	12 months	Fever, generalized tonic convulsion, sialorrhea, rhonchus	Leukopenia, anemia, thrombocytopenia	Not done	Convulsive syndrome	Positive	Negative	Cloudy and bloody liquid. Negative for leukocytes. RBC 195.000/mm3, Glucose (76 mg/dL), Proteins (72.3 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+) DENV-1

Code	Age	Clinical Findings	Laboratory Findings	Images	Presumptive diagnosis	Dengue IgM	Dengue IgG	Cerebrospinal fluid analysis	Virology Test
795	12 months	Tonic-clonic seizures, fever, vomiting, cough, tachypnea, rhonchus, skin and mucosae pallor, sialorrhea	Leukopenia, anemia, thrombocytopenia	Not done	Convulsive syndrome Acute pharyngitis Viral encephalitis	Positive	Negative	Clear liquid, Leukocytes 98/mm3, Glucose (44 mg/dL), Proteins (64.9 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+)
941	5 years	Ataxia, fever, generalized abdominal tenderness, cough	Normal	Simple brain CAT scan normal	Ataxia, Postinfectious Cerebellitis	Positive	Negative	Clear liquid, with no RBC, leukocytes 4/mm3, Glucose (48 mg/dL), Proteins (25.8 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+)
308	5 years	Fever, Seizures, Asthenia, adynamia, rash, petechiae, headache, vomiting,	Leukopenia, thrombocytopenia, leucopenia, Increased ALT value	Chest Rx normal, Simple brain CAT scan normal	Dengue with warning signs, Vasculitis	Positive	Negative	Clear liquid, RBC 220.000/mm3, leukocytes 3000/mm3, Glucose (56 mg/dL), Proteins (55.7 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+)
925	7 years	Fever, tonic-clonic seizures, sphincters relaxation, asthenia, adynamia, irritability, vomiting, hepatomegaly	Thrombocytopenia - PTT prolonged	Simple brain CAT scan normal	Dengue with warning signs. Epilepsy	Positive	Positive	Not done	RT-PCR (+) DENV-1

Code	Age	Clinical Findings	Laboratory Findings	Images	Presumptive diagnosis	Dengue IgM	Dengue IgG	Cerebrospinal fluid analysis	Virology Test
329	7 years	Fever, vomiting, diarrhea, tachycardia, hypotension, mucosa and skin pallor, hepatomegaly, low blood pressure, respiratory distress (intercostal retractions, nasal flaring, basal rales), Hypoactivity, stupor,	Hematocrit reduction, creatinine value reduction	Brain resonance normal, mastoiditis	Viral encephalitis, gastroenteritis, acute respiratory infection	Positive	Negative	Clear liquid, with no RBC, leukocytes 720/mm3, Glucose (49 mg/dL), Proteins (155 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative.	RT-PCR (+)
210	10 years	Headache, Fever, nauseas, ataxia, vomiting, hyporeflexia, epistaxis, asthenia, irritability	Not available	Simple brain CAT scan with no alteration	Acute ataxia, Viral cerebellitis	Positive	Positive	Clear liquid, RBC 20/mm3, leukocytes 90/mm3, Glucose (44 mg/dL), Proteins (68 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative	RT-PCR (+)
797	10 years	Fever, tonic-clonic seizures, epistaxis, dehydration, irritability	Leukopenia, thrombocytopenia, PTT prolonged, AST value increased	Simple brain CAT scan normal, Electroencephalogram normal, chest Rx normal	Convulsive syndrome	Positive	Negative	Clear liquid, with no RBC or leukocytes, Glucose (71 mg/dL), Proteins (21.4 mg/dL). Negative test for *H. influezae, S. pneumoniae*, group B *Streptococcus, N. meningitidis. Criptococus neoformans* negative, *M. tuberculosis* negative	RT-PCR (+)

Clinically, eight patients presented tonic-clonic seizures although only 2/11 reported headache and three developed consciousness alteration or irritability, two had ataxia symptoms and one develop unilateral paresis. Other found signs were vomiting (5), hepatomegaly (5), cough (5), abdominal pain (3), asthenia (3) and epistaxis (2). None of the patients presented plasma leakage signs such as edema or pleural effusion, nor altered transaminases values. There was brain tomography in eight patients and one magnetic resonance, all showing no alterations. Additionally, chest Rx from three patients were normal. Despite the severity, there was no fatal cases, and all of them, but one, recovered without sequelae.

The hematimetric analysis indicated anemia, and low hematocrit in all patients (median 33.5%, IQR 31.8–34.6%) since children normal value is 36%-42%. A mild leukocytosis was observed at day one and a decrease until day four when leukopenia was evident. Six patients developed thrombocytopenia being at day sixth the lowest value (median 99.200 platelets/mm^3). The coagulation prothrombin test only showed a 15.4 s prolonged at the first hospitalization day. However, the partial thromboplastin time (PTT) was prolonged during six hospitalization days with values between 32.3 and 35.1 s (Table 2). Transaminase levels used to evaluate the hepatic function and AST showed a slight increase during the last three hospitalization days (fifth to the seventh day), but the values were close to those reference levels while ALT did not show changed levels. There were no changes in renal function markers in any of the patients.

Table 2
Hematologic parameters description according hospitalization day (mean (IQR) [n=])

	Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Blood parameters	Hemoglobin (mg/dL)	11.5 (11.2–11.9) [7]	10.7 (10.3–11.6) [6]	10.4 (10-10.4) [6]	11.5 (10.9–12.2) [6]	10.8 (9.6–12.2) [5]	11.5 (10.5–13.2) [6]	11.6 (11.4–12.3) [5]
Median (IQR) [n=]	Hematocrit (%)	33.8 (33.5–36.8) [7]	32.5 (31.1–34.2) [6]	31.8 (31-32.5) [6]	33.9 (32.2–35.5) [6]	32.6 (29.3–35.5) [5]	34.6 (32.6–39.6) [6]	33.5 (33.4–35) [5]
	Leukocytes (x 1000 cell/ µL)	9.8 (5.9–13.9) [8]	7.5 (5.1–8.8) [6]	6.8 (4.0-11.1) [7]	3.6 (2.8–4.8) [6]	5.1 (2.7–6.5) [6]	5.7 (1.8–8.4) [6]	8.4 (6.0-7.2) [5]
	Neutrophils (%)	56 (41–71) [8]	45.6 (31–60) [6]	42.5 (30–51) [6]	36.6 (28–43) [6]	38.6 (35–51) [6]	32.6 (18.2–43.4) [6]	35.8 (32–37) [5]
	Lymphocytes (%)	33.9 (19.6–46.8) [8]	47.1 (33–62) [6]	48.9 (87.9–60.3) [6]	52.1 (43–69) [6]	51.8 (36–57) [6]	53.2 (37–67) [6]	40.3 (31–56) [5]
	Platelets (x1000 cell/ µL)	184.8 (109–230) [7]	251.8 (130–372) [7]	266.8 (180–380) [6]	199.1(105–207) [6]	169.2 (88–211) [5]	99.2 (80–88) [5]	271.4 (85–457) [5]
Clinical Laboratory values	PT (seg)	*15.4 (2.3) [5]	13.5 [1]	13.8 (0.6) [2]	13.7 (2.7) [3]	14.2 (1.6) [6]	12.7 (1.1) [4]	13.2 (0.5) [3]
Mean (SD) [n=]	PTT (seg)	*35.1 (8.9) [5]	*37.9 [1]	29.8 (2.4) [2]	*32.9 (5.6) [3]	*32.3 (8.1) [6]	*32.66 (5.7) [3]	*37.1 (1.0) [4]
	AST (UI/mL)	*66.9 (35.9) [3]	*78.9 (14.4) [2]	59.3 [1]	50.4 (21.1) [3]	*82.4 (52.5) [4]	*83.1 (43.4) [4]	*108.5 (78.1) [2]
	ALT (UI/mL)	75.9 (96.6) [3]	90.4 (96.6) [2]	28.2 (12.4) [2]	23.4 (6.1) [3]	35.2 (12.3) [5]	48.3 (20.9) [4]	49.5 (18.1) [3]
	BUN (mg/dL)	4.45 (1.3) [2]	NA	2.75 (0.4) [2]	NA	5.4 (6.1) [2]	3.6 [1]	9.9 (0.1) [2]
	Creatinine (mg/dL)	0.29 [3]	0.38 [1]	0.27 [2]	0.2 [1]	0.36 [3]	0.27 [1]	0.52 [1]

*.- Significant differences between values in different hospitalization days, NA not available.

Discussion

Colombia has seen an increase in the dengue cases number in the last decade with higher severity and mortality [4, 5], forcing to medical personnel and health authorities to strengthen capacities to recognize and differentiate the classical dengue signs and symptoms from the atypical and severe presentation. After the redefinition of diagnostic and severity criteria by WHO [21] the severe dengue is defined when the patients present organ damage associated signs (liver, brain, kidney) or hypovolemic shock or massive bleeding. This system facilitates the early recognition of most severe cases for reducing the mortality numbers.

This study presented eleven severe dengue cases in children between eight months to 10 years old, living in the Colombian Huila province, a hyperendemic area that reported two-fifths of severe dengue cases registered from 2000 to 2011 [5]. All the patients presented brain compromise, nine diagnosed as encephalitis (81.8%) following the criteria described previously [22], such as: fever, sensory disturbances, seizures or focal neurological signs, but also positive tests (IgM or NS1) or RT-PCR in serum or CSF and negative for others encephalitis causes. This presentation was the most common compromise in this series, characterized by seizures in six patients (tonic-clonic convulsions) as has been previously reported in children [23]. There was one severe sensory impairment case, and another presented with severe headache, which also is frequently described in dengue encephalitis [24]. Less than half of the described patients develop classical dengue signs like vomiting, hepatomegaly, and exanthem, indicating the neurological cases do not seem dengue disease, and that nervous signs could appear alone leading to under registration of severe cases and possibly in delay of the establishment of adequate treatment [22]. Two patients were diagnosed as cerebellitis, characterized by nystagmus, dysarthria, or ataxia, which also has been reported previously [25]. Fortunately, there were no fatal cases in this patient group; on the contrary outcomes and recovery were satisfactory.

It is recommended that in DENV circulation areas, those patients with fever and neurologic signs be investigated for dengue disease ensuring the laboratory confirmation using both serology or molecular tests, that together could offer high sensitivity [26]. Here, we use both IgM and IgG serology in addition to RT-PCR, and found all serum samples positive, even serotyping DENV-1 in three patients, which is not the most reported associated with neuroinfection [27]. The finding of nine sera negative for IgG is very odd, because most of the severe dengue cases are during secondary infections with a different serotype, where the antibodies are not capable of the second virus neutralization but induce an enhanced infection and an aberrant immune response. Therefore, severe dengue with a primary compromise of an organ in a primoinfection could suggest a neurotropic strain or a host characteristic that determine the neuroinfection in this children group.

All the CSF samples were negative for bacteria or fungus, but five out of nine had lymphocyte pleocytosis an uncommon sign in dengue encephalitis, since most of the cases do not develop CSF anomalies [23], even three quarters of dengue encephalitis or meningitis patients showed normal values in CSF analysis [27]. Despite, previous studies reported that brain tissue damage detectable by tomography images, children described in this work did not present anomalies.

Although it is preferable to use magnetic resonance for brain evaluation because the accuracy of this technique, but regularly imaging abnormalities during dengue encephalitis are not specific [28] and are still poorly defined [29, 30], although ischemia or hemorrhages must be sought. On the other hand, we found normal leukocyte counts instead of the classical leukopenia of the dengue warning signs or severe dengue, which pose a difficulty to early diagnosis, although there was thrombocytopenia only at day six of hospitalization with no changes in ALT and AST transaminases as reported previously.

Conclusion

This children group were diagnosed as severe dengue with central nervous system manifestations without shock typical signs or hemorrhages. Therefore, we should recommend that in endemic dengue areas, health professionals should include infections by this virus in those patients with fever and neurological manifestations as part of the primary diagnostic and must be vigilant to neurological signs that could appear after the acute dengue disease.

Limitations

This study was retrospective and is limited by its observational nature. Although we enrolled almost all those children with severe dengue diagnosis in this Hospital, detailed clinical and laboratory information was obtained from these reported patients after an in-depth search of data in the medical records.

List Of Abbreviations

DENV, dengue virus

NS1, DENV nonstructural protein 1

CSF, cerebrospinal fluid

CNS, central nervous system

BBB, blood-brain barrier

TNF, tumor necrosis factor

WHO, World Health Organization

RT-PCR, reverse transcription – polymerase chain reaction

PTT, partial thromboplastin time

AST, aspartate aminotransferase

ALT, alanine aminotransferase

Declarations

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Conflict of interest

The authors have no financial or other interests regarding the submitted manuscript that might be construed as a conflict of interest.

Availability of data

The dataset supporting the conclusions of this article isavailable in the www.researchgate.netrepository, DOI: 10.13140/RG.2.2.32618.54728 and DOI: 10.13140/RG.2.2.15841.33128

Author contributions

Jaime E. Castellanos: Principal investigator, Data analysis, manuscript writing and editing.

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Gladys Acosta: Clinical evaluation, brain images analysis, laboratory data analysis, sample collection, manuscript editing.

Doris Salgado: Clinical evaluation, brain image analysis, sample collection, manuscript writing and editing.

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Sigrid Camacho-Ortega: Serum sample processing, molecular diagnosis, writes manuscript draft.

Eliana Calvo: Serum sample processing, dengue molecular diagnosis, manuscript editing

Myriam Velandia-Romero: Co-Investigator, data analysis, manuscript revision.

Ethics approval and consent to participate

This study was approved by both the Institutional Review Board of Hospital Hernando Moncaleano Perdomo Parents signed an informed consent form. Names and characteristics of each patient were blinded and coded to ensure their privacy.

Declaration section

This research was revised an approved by the Ethic's Institutional Review Board of Universidad El Bosque (Minute 007-2014). Consent to publish are not applicable.

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