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Is it possible to identify dengue in children on the basis of Ministry of Health criteria for suspected dengue cases?

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Abstract

Objectives: To identify clinical characteristics indicative of dengue and to evaluate the applicability to children of the Health Ministry criteria for suspected cases.

Methods: A cross-sectional study undertaken at the General Pediatrics Center of the *Fundação Hospitalar de Minas Gerais*. Children were enrolled if presenting acute febrile conditions with no definite etiology, lasting > 24 hours and ≤ 7 days and if resident in the Metropolitan Region of Belo Horizonte. Clinical variables were investigated, specific tests were performed and aspartate-aminotransferase assayed, during a period considered both endemic and epidemic for the disease. The subset of children who did have dengue was compared with the subset of nonspecific acute febrile diseases. The Health Ministry criteria for suspected cases was evaluated.

Results: Dengue was diagnosed in 50.4% of the 117 children studied. There were no statistically significant associations between the disease and the majority of the symptoms analyzed. Only exanthema was more often associated with dengue (Prevalence Ratio = 1.49; 95% CI: 1.05-2.11). The criteria for suspected cases of dengue had a sensitivity of just 50.8% and a positive predictive value of 62.5%. These values were greater among schoolchildren and during the period of greater disease incidence.

Conclusions: Dengue is common among febrile diseases of childhood, with prevalence that varies according to the epidemiological situation. The clinical status of children with dengue was very similar to that of children with other nonspecific diseases. The Health Ministry criteria for suspected cases were shown to be of little use, particularly with smaller children and during periods of reduced incidence.

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Introduction

Dengue is currently a serious public health problem in Brazil. Infection by the dengue viruses (serotypes DEN-1, DEN-2, DEN-3 and DEN-4) leads to variable clinical manifestations, with possible reactions ranging from asymptomatic infection or undifferentiated fever to severe forms with hemorrhage and/or shock. Clinical cases can be divided into three main groups: a) classic dengue; b) dengue hemorrhagic fever/dengue shock syndrome - DHF/DSS; c) dengue with complications.[1]

According to the Health Ministry, a suspected case of classic dengue presents with fever lasting a maximum of 7 days, together with at least two of the following symptoms: headache, retroorbital pain, myalgia, arthralgia, prostration,

exanthema. In addition to these symptoms, the patient must have been in an area where dengue is being transmitted or where *Aedes aegypti* is present during the previous fifteen days.

The World Health Organization (WHO) estimates an annual occurrence of twenty million cases of dengue infection. In many countries dengue mainly affects children and in tropical Asia it is open of the main causes of infant death and hospital admission.[2] The first dengue epidemic in Brazil to be documented both clinically and by laboratory findings was in 1981/82 in Roraima.[3] In Belo Horizonte, the first cases of dengue were registered in 1996. In 1998 there was a large-scale epidemic, followed by an endemic period during 1999 and 2000.[4] Incidence rates of the disease in the city have always been highest during the first six months of the year. In 2002, more than 150 dengue cases a week were diagnosed between February and May, with just 6% being in children.[5]

The majority of dengue infections in children are asymptomatic or oligosymptomatic. A study in Thailand demonstrated that 87% of dengue infections resulted in juts one day's absence from school.[6] A serological survey undertaken in Rio de Janeiro found positive serology in 33% of schoolchildren, despite parents having said their children had not had the disease.[7]

With children it is often difficult to differentiate dengue from other acute febrile diseases. A study of Thai children with flushed faces and short-term undifferentiated fever diagnosed dengue in 35% of the children,[8] while in an earlier study performed during an epidemic period, this rate was 90%.[9] In Pakistan, the frequency of dengue among children with short-term fever of indefinite etiology was 26%.[10] In several studies, the classic symptoms of dengue (headaches, arthralgia, myalgia) were found with similar frequency in children with dengue and children with other febrile diseases.[11-13] In Cuba, during the epidemic outbreak of 1997, exanthema was the most common sign among children hospitalized with dengue.[14]

Laboratory workup is of supreme importance to confirming dengue diagnoses in children. The two basic methods of laboratory diagnosis are detection of either the virus or antibodies to it. Viral genome detection by means of polymerase chain reaction (PCR) using reverse transcriptase has been employed with success by several different laboratories and has proven useful for dengue diagnosis.[15-17] The most used serological tests are hemagglutination inhibition and immunoenzymatic IgM capture (ELISA-IgM). The second of these is quick and simple and in the majority of cases dengue can be confirmed with a single serum sample taken after the sixth day of the disease, as long as this is associated with clinical and epidemiological status.[3] Taking hemagglutination inhibition as the gold standard, the sensitivity of ELISA-IgM reaches 90 to 97%. False-positive reactions may occur in less than 2% of cases and some false-negatives may be observed in secondary infections.[16]

In addition to serological and/or virological tests for disease confirmation, there are nonspecific tests with high positive predictive values, such as increased aminotransferases.[18-20] The hematological abnormalities, increased hematocrit and reduced platelets are essential for DHF to be diagnosed.

In the face of the endemic-epidemic dengue situation in Belo Horizonte and the nonspecific nature of symptoms in children, the present study was undertaken with the objective of assessing the applicability to children of the criteria for suspected cases of dengue stipulated by the Health Ministry and to identify clinical signs and symptoms that are of help in differentiating dengue from other febrile diseases of childhood.

Methods

This was a cross-sectional study, performed at the walk-in clinic at the General Pediatrics Center (GPC) of the *Fundação Hospitalar de Minas Gerais* (FHEMIG). Children were enrolled if they were aged from one to 12 years, had an acute febrile condition of indefinite etiology with a duration of at least 24 hours and less than or equal to 7 days and were residents of the Metropolitan Region of Belo Horizonte.

The study was performed in two stages, the first during a period considered epidemic (20 March to 19 July, 2002) and the second during an endemic period (2 October 2002 to 31 January 2003). For a four-hour period from Monday to Saturday, those children treated at the GPC clinic that met the research inclusion criteria were sent for data collection by trained fifth-year medical students who, after an interview, filled out standardized investigation forms. The following variables were recorded: duration of fever, presence or absence of headache, retroorbital pain, myalgia, arthralgia, prostration, exanthema, diarrhea, vomiting, facial flush, irritability, sore throat, coryza, coughing, abdominal pains, dehydration, manifestations hemorrhagic, symptoms neurological, hepatomegaly. For smaller children a detailed interview attempted to find any indication of symptoms. A pilot study was performed and its results were used to ensure that the questionnaire and fieldwork were suitable.

At the original consultation, aspartate-aminotransferase (AST) assays were performed together with specific dengue tests (PCR and IgG for children whose fevers had lasted up to 5 days, IgM and IgG for children with fever for more than 5 days). The laboratory tests were performed at the Medical Faculty/UFMG: specific tests (serological and PCR) at the Diagnostic Research and Support Center (DRSC) and AST assays at the Central Laboratory. Blood was taken at the GPC laboratory, centrifuged, and serum was sent to the DRSC, together with a copy of the investigation form and within a maximum of 4 hours. The serological method employed was the Dengue Ultramicroelisa (UMELISA) developed by the Cuban Immunoassay Center.[21,22] This is a heterogenous immunoenzymatic test, it its capture phase, which uses ultramicroELISA strips sensitized with antibodies against human IgM or IgG as its solid phase. The sample is incubated in the cavities of the strip, and any IgM or IgG present in the sample attach to the antibodies. Monoclonal

mouse antigen against the dengue virus, conjugated with alkaline phosphatase is added and will join with the result of the previous reaction if the result is positive. A fluorigenic substrate is added and the intensity of fluorescence allows the presence of specific dengue antibodies to be characterized. Positive and negative controls are employed. The sample is defined as positive above 0.300 with the DENGUE IgM UMELISA,[23] and above 0.150 for the DENGUE IgG UMELISA.[24] For PCR testing, the primers developed by Lanciotti et al.[15] were used with internal positive controls. The upper limit of normality was set at 55 U/l of AST.[23]

When the patient returned, after the sixth day of the disease, a physician investigated signs and symptoms that had appeared during the disease and serology (IgM) was investigated in cases for which it had not yet been ascertained. If the initial consultation had taken place on the sixth or seventh day then no appointment was made for heir return. The interval between the first consultation and the return appointment varied from one to 20 days (a mean of 7 days). Since daily observations were not made of the patients, the details recorded were aimed at validating the detection of symptoms at the first interview and at verifying if further symptoms had appeared as the disease progressed. In order to facilitate attendance at the follow-up appointment, transport tokens were supplied. The test results were later communicated to patients' families by telephone.

Children whose PCR and/or IgM were positive were defined as dengue cases. The subset of children with dengue was compared with the group of children with nonspecific acute febrile conditions. The Health Ministry criteria for suspected cases was evaluated and its sensitivity and predictive value for the pediatric age group.

For the analysis of associations between the variables and dengue, prevalence ratios were used to estimate the magnitude of association between certain signs and symptoms and the disease. The limit for statistical significance was defined as $p < 0.05$. Data was analyzed using Epi-Info, version 6.04.

The study was approved by the Ethics Committee at the *Universidade Federal de Minas Gerais* (UFMG). Informed consent was obtained in writing from those responsible for the children.

Results

Initially 125 children were selected. Eight children were excluded: one was not a resident of the Metropolitan Region of Belo Horizonte, four were less than one year old, one had fever for more than 7 days and in two cases the study protocol was not followed. Fifty-nine percent (n = 69) of the 117 children studied (50 in the first stage and 67 in the second stage) were male, 53% (n = 62) were aged 1 to 4 years and 47% (n = 55) from 5 to 12 years.

Fifty point four percent (n = 59) of the children studied were diagnosed with dengue, with 62% (n = 31) being positive during the first stage and 41.8% (n = 28) in the second. If the period of greatest incidence is taken in isolation (20 March to 20 May, 2002), 64.1% of febrile children enrolled on the study had dengue, and, during the period of lowest incidence (2 October to 2 December, 2002), this figure was 30.2%. The PCR test was positive in 35 cases. Three serotypes were detected, of which 80.0% (n = 28) were DEN-2, 11.4% (n = 4) were DEN-1 and 8.6% (n = 3) were DEN-3. The IgG test was performed at the first consultation in 83.8% (n = 98) of cases, being positive in 14 children. Eight of these were diagnosed with dengue in the present study and recovered with no complications. One fact that drew attention was that just two children had been diagnosed with dengue on a previous occasion.

Table 1 presents the main signs and symptoms detected among the children with acute febrile conditions during the first consultation. It was found that there was no statistically significant association between the disease and the majority of the symptoms analyzed. Headache, retroorbital pain, myalgia and arthralgia, all of which are symptoms typically attributed to dengue, occurred with similar frequency in the two groups. Prostration was present in almost 80% of the children, irrespective of diagnosis. Only exanthema was more associated with dengue ($p = 0.08$). The prevalence of dengue was 1.49 times greater among cases with exanthema. Sore throat, coryza and coughing, all symptoms typical of acute respiratory diseases, were also exhibited by the children with dengue. Hemorrhagic manifestations were infrequent. The tourniquet test was performed on 74 children and was positive in 13.5% of the dengue cases and in 5.4% of the nonspecific febrile diseases. Aspartate-aminotransferase was assayed in 84 cases. The prevalence of dengue was 1.64 times greater (95% CI: 1.04-2.58) among children with elevated AST. In some of the dengue cases AST reached values above 1,000 U/l.

The distribution of symptoms was evaluated for the age groups 1 to 4 years of age and 5 to 12 years. It was found that there was no statistically significant association between any of the symptoms investigated and dengue. Similarly, when the simultaneous presence of two of the symptoms in the criteria for suspected cases of dengue (headache, retroorbital pain, myalgia, arthralgia, prostration and exanthema) was analyzed, no statistically significant association was found.

Table 2 presents the results pertaining to those children who attended the follow-up appointment (n = 99), making it possible to evaluate the presence of symptoms over the whole disease period. The majority of symptoms continued to have no significant association with dengue. Prostration and headache continued to be the most common symptoms, both for the subset with dengue and for those with other febrile diseases. The strongest association with dengue was for exanthema (Prevalence Ratio = 1.53; 95% CI: 1.07-2.19), with a p value of 0.06.

The children with dengue and those without were comparable in terms of age. The median age for both groups was 4 years and the Kruskal-Wallis test returned a non-significant value ($p = 0.10$).

When classifying children according to the Health Ministry criteria for suspected cases, a significant association was observed between having the disease and

fulfilling the criteria (p = 0.05), with a prevalence 1.49 times greater (95% CI: 1.04-2.12). However, if diagnosis had been based on these criteria, 49.2% of the children who did have dengue would not have been identified. Among the subset of children aged one to 4 years, the association was not statistically significant. In the 5 to 12

Table 1 - Symptoms and signs detected in children ranging from 1 to 12 years-old, with and without dengue, at the first consultation

Symptoms	With dengue n (%) (n = 59)	Without dengue n (%) (n = 58)	PR *	CI 95%	p
Headache	37 (62.7)	36 (62.1)	1.01	(0.70-1.47)	0.91
Retroorbital pain	17 (29.3)	11 (19.0)	1.30	(0.90-1.89)	0.28
Myalgia	23 (39.7)	18 (31.0)	1.20	(0.84-1.73)	0.44
Arthralgia	11 (19.0)	13 (22.4)	0.90	(0.53-1.45)	0.82
Prostration	47 (79.7)	46 (79.3)	1.01	(0.65-1.58)	0.86
Exanthema	17 (28.8)	8 (13.8)	1.49	(1.05-2.11)	0.08
Diarrhea	10 (16.9)	11 (19.0)	0.93	(0.57-1.52)	0.97
Vomit	35 (59.3)	28 (48.3)	1.25	(0.89-1.81)	0.31
Epistaxis	7 (11.9)	9 (15.8)	0.84	(0.47-1.51)	0.73
Flushing	22 (37.3)	19 (33.3)	1.09	(0.75-1.57)	0.80
Irritability	20 (33.9)	11 (19.3)	1.41	(0.99-1.99)	0.11
Sore throat	14 (23.7)	18 (31.6)	0.82	(0.53-1.27)	0.46
Coryza	22 (37.3)	28 (49.1)	0.78	(0.54-1.15)	0.27
Cough	28 (47.5)	29 (50.9)	0.93	(0.65-1.34)	0.86
Abdominal pain	14 (23.7)	7 (12.1)	1.42	(0.98-2.06)	0.16
Gengivorrhagia	2 (3.4)	1 (1.7)	1.33	(0.59-3.03)	1.00
Petechiae	2 (3.4)	3 (5.2)	0.79	(0.26-2.33)	0.68
Intestinal bleeding	2 (3.4)	2 (3.4)	0.99	(0.37-2.69)	1.00
Dehydration	2 (3.4)	5 (8.8)	0.55	(0.17-1.79)	0.27
Neurological symptoms	1 (1.7)	2 (3.4)	0.66	(0.13-3.28)	0.62
Hepatomegaly	1 (1.7)	2 (3.4)	0.66	(0.13-3.28)	0.62

* PR = prevalence ratio.

Table 2 - Symptoms and signs detected in children with and without dengue in the follow-up visit (after sixth days of the symptoms onset). Belo Horizonte, 2002/2003

Symptoms	With dengue n (%) (n = 51)	Without dengue n (%) (n = 48)	PR *	CI 95%	p
Headache	36 (70.6)	30 (62.5)	1.20	(0.78-1.85)	0.52
Retroorbital pain	16 (31.4)	11 (22.9)	1.22	(0.82-1.81)	0.47
Myalgia	22 (43.1)	18 (37.5)	1.12	(0.76-1.64)	0.71
Arthralgia	11 (21.6)	11 (22.9)	0.96	(0.60-1.54)	0.94
Prostration	42 (82.4)	40 (83.3)	0.97	(0.59-1.59)	0.89
Exanthema	18 (35.3)	8 (16.7)	1.53	(1.07-2.19)	0.06
Diarrhea	11 (21.6)	9 (18.8)	1.09	(0.69-1.71)	0.92
Vomit	33 (64.7)	24 (50.0)	1.35	(0.89-2.04)	0.20
Flushness	18 (35.3)	18 (37.5)	0.95	(0.64-1.43)	0.98
Irritability	17 (33.3)	9 (18.8)	1.40	(0.97-2.04)	0.16
Sore throat	16 (31.4)	14 (19.2)	1.05	(0.70-1.58)	0.98
Coryza	24 (47.1)	23 (47.9)	0.98	(0.67-1.44)	0.91
Cough	27 (52.9)	28 (58.3)	0.90	(0.61-1.32)	0.74
Abdominal pain	21 (41.2)	14 (29.2)	1.28	(0.88-1.86)	0.30
Petechiae	3 (5.9)	2 (4.2)	1.18	(0.56-2.47)	0.94

* PR = prevalence ratio.

years age range, the association between having the disease and fulfilling the criteria was significant (p = 0.04). Notwithstanding, even in this age group, if diagnosis had been based on the Health Ministry criteria for suspected cases, then 33.3% of children who did have dengue would not have been identified (Table 3).

The applicability of the criteria for suspected cases was evaluated for the different age groups and seasons. The sensitivity of the suspected dengue case criteria was 50.8%, and specificity and positive predictive value were 69 and 62.5%, respectively. Sensitivity and positive predictive value were better among schoolchildren and during the period of greatest dengue incidence (Table 4).

Discussion

The results of this study indicate that dengue is common among the acute febrile diseases of childhood and that this prevalence varies in accordance with epidemiological status. It was found that greatest prevalence occurred during the period in which the Municipal Department of Health recorded more than 200 cases of dengue weekly, indicating that this was an epidemic period. It is probable that there is significant under-reporting. Furthermore dengue is often asymptomatic in children,[7,24] as is shown by the fact that the majority of children whose IgG had been positive at their first appointment had not been described as having suffered from dengue before.

In this study the clinical status of children with dengue diagnoses was very similar to that of children with other nonspecific acute febrile conditions. An earlier study had shown that there was no significant difference in the frequency of headache, abdominal pains and hemorrhagic manifestations between children with dengue and those with other febrile diseases that are accompanied by facial flush, but that children with dengue exhibited with greater frequency anorexia, nausea and vomiting and were more often positive when tested with the tourniquet test and for thrombocytopenia, leukopenia and elevated AST and ALT.[8] Another study confirmed that the group of symptoms classically associated with dengue (headache, arthralgia, myalgia, exanthema, prostration) were observed little among children and that their frequency was similar for cases of dengue and other febrile diseases; headache, coryza, coughing and diarrhea were significantly more frequent with nonspecific febrile diseases while exanthema was more common in dengue.[11] A similar comparison was undertaken in Vietnam: symptoms classically attributed to dengue had

Table 3 - Diagnosis and fulfillment of criteria for suspected cases by age range in children with acute fever. Belo Horizonte, 2002/2003

Age (years)	Fulfillment of criteria for suspected cases				PR *	CI 95%	p
	Yes		No				
	With dengue	Without dengue	With dengue	Without dengue			
1 to 4	12	8	20	22	1.26	0.78-2.03	0.52
5 to 12	18	10	9	18	1.93	1.06-3.52	0.04
Total	30	18	29	40	1.49	1.04-2.12	0.05

* PR = prevalence ratio.

Table 4 - Validity of criteria for dengue suspected cases in different age ranges and stages. Belo Horizonte, 2002/2003

Variables	Sensitivity (%)	PPV * (%)
Age (years)		
1 to 12	50.8	62.5
1 to 4	37.5	60.0
5 to 12	66.7	64.3
Periods		
Initial period of the 1st stage †	68.0	89.5
Initial period of the 2nd stage ‡	15.4	16.7

* PPV = positive predictive value.
† March 20, 2002 to May 20, 2002.
‡ October 02, 2002 to December 02, 2002.

similar frequencies for both groups, and the group with dengue presented less respiratory symptoms and more gastrointestinal symptoms.[13]

In the present study, only exanthema exhibited an association close to significance. A literature review undertaken in Uberlândia, despite covering all age groups , corroborates this finding.[12] If symptoms described for the children who attended the second appointment are considered, the strength of this association increases, providing evidence that in many cases exanthema is not manifest in the first days of the disease. It should be emphasized, however that the results observed with no statistical significance may be the result of the small sample size. Elevated AST was more common among the children who did have dengue, reaching extremely high levels in certain cases, which reinforces the importance of liver involvement in this disease.[18,19,25] There were no differences in the occurrence of dengue and other febrile diseases with respect of age group, which is in contrast with a study by Kalayanarooj et al., in Thailand, which found evidence of greater dengue frequency among older children.[8] It was found that even among them, the clinical status of dengue is very similar to that of other nonspecific febrile diseases, which is in contrast with the belief that among schoolchildren symptoms would be similar to adults'.[2,16]

In the present sample there were no cases that fulfilled the criteria for DHF, and just eight children had secondary infection. However, hemoconcentration and thrombocytopenia could not be correctly evaluated because the blood test was not requested for some children. Hemorrhagic manifestations, hepatomegaly and positive tourniquet tests were infrequent and there were no significant differences between the two groups.

In the present study a diagnosis of dengue was defined as a positive PCR and/or IgM test. Cases with positive IgM for a single sample would be "probable" dengue cases since the finding can persist for up to 90 days. Despite this, "probable" and "confirmed" cases have been analyzed in conjunction in some studies[14,26,27] and the Health Ministry defines confirmed cases of dengue as those in which IgM is positive in association with indicative clinical and epidemiological status.[3] According to that definition, around 50% of the children with acute nonspecific febrile diseases had dengue. The Health Ministry criteria for suspected cases was shown to be of little use, particularly for children less than 5 years old and outside of epidemic periods. If diagnosis had been based on these criteria, nearly half of the children with dengue would not have been identified. A greater difficulty with diagnosis during non-epidemic periods has also been reported in an earlier study.[28]

Worthy of note was the fact that three serotypes were found to be circulating simultaneously, which is an epidemiological situation of increased risk for DHF. This fact reinforces the need for vigilance and actively seeking out cases so that the disease can be opportunely identified. One of the measures set out by the WHO is the vigilance of fever,[2] so that sentinel clinics notify the sanitary vigilance authority weekly of the number of febrile patients they have seen, in order to detect abnormal increases in febrile diseases. Another strategy is to perform specific dengue tests on serum samples collected routinely by programs for the eradication of exanthematic diseases and also, periodically, on samples of children with acute nonspecific febrile conditions.

In synthesis, the results of this study indicate that it is very difficult to clinically differentiate dengue from other febrile diseases of childhood, and clinical findings must not be dissociated from epidemiology. Laboratory support is essential with this age group, particularly during periods of low incidence. Healthcare professionals must be constantly informed of the epidemiological status of the disease, and remain alert in the face of acute febrile conditions of indefinite etiology for early diagnosis and suitable follow-up.

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