

ORIGINAL ARTICLE

Validation of the Modified Faine's Criteria in the Diagnosis of Leptospirosis in Children Using the Microscopic Agglutination Test as the Gold Standard

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ABSTRACT

Objective

This study aimed to validate the modified Faine's criteria (Parts A and B) proposed by Brato in the early diagnosis of leptospirosis in children using the microscopic agglutination test (MAT) as gold standard.

Methodology

This diagnostic validity study was conducted at the Philippine General Hospital. It included all pediatric patients who were admitted between September 2009 to December 2010 and who satisfied the presumptive and suggestive criteria in the diagnosis of leptospirosis based on the modified Faine's criteria. A fourfold or greater rise in paired MAT titers was used as the gold standard. Calculations for sensitivity, specificity, positive and negative predictive values, and likelihood ratios of positive and negative tests were computed.

Results

Thirty-three patients satisfied the diagnosis of leptospirosis based on the criteria; however, only 20 of these had paired MAT titers and were included. The modified Faine's criteria had a sensitivity of 60%, specificity of 73%, positive predictive value (PPV) of 43%, negative predictive value (NPV) of 85%, positive likelihood ratio of 2 and negative likelihood ratio of 0.4. Modifying the clinical criteria by revision of the point allocation to create a "Pediatric Locally Modified Criteria" increased the sensitivity to 80%, PPV to 50%, NPV to 92%, positive likelihood ratio to 3 and negative likelihood ratio to 0.3.

Conclusion

The Modified Faine's criteria had poor sensitivity and low positive predictive value and cannot be recommended as a screening test for the early diagnosis of leptospirosis in children. A proposed modification of the clinical criteria for local application increased diagnostic accuracy but must be further validated in a larger number of pediatric patients in the Philippines.

INTRODUCTION

Annual incidence of the disease is estimated at 0.1-1 per 100,000 in temperate climates and 10-100 per 100,000 in the humid tropics. Major outbreaks of the disease in South East Asia due to floods were reported in Jakarta in 2003 and in Mumbai in 2005.¹ In the Philippines, the annual incidence is 0.2-0.6 per 100,000,² except during the onslaught of typhoon Ondoy (known internationally as Ketsana) when there was an outbreak of leptospirosis. Three hundred twenty three deaths were reported, mostly coming from the National Capital Region (NCR) and affecting those from the 19-to-64 year old age group. The pediatric population was not spared, with 1,073 cases reported.²

The microscopic agglutination test (MAT) is considered the "gold standard" or cornerstone of serodiagnosis for leptospirosis because of its unsurpassed diagnostic (serovar/serogroup) specificity in comparison with other currently available tests such as macroscopic slide agglutination test, microcapsule agglutination test and latex agglutination tests. On the other hand, the MAT also has its disadvantages, such as the need for facilities to culture and maintain panels of live leptospire. Furthermore, the test is both technically demanding and time-consuming, particularly when the panel is large.³

The World Health Organization (WHO), in recognizing that laboratory tests are rarely helpful in the early diagnosis of leptospirosis, came up with the Faine's criteria which mainly include the scoring of clinical and epidemiological history of a patient (Parts A and B) while being supported by laboratory parameters (Part C).⁴ Positive serology for leptospirosis using single or paired serum is included in the laboratory criteria but the definitive diagnosis of leptospirosis requires the isolation of leptospire in culture from any clinical specimen. A total score of 26 or more from Part A or Parts A and B suggest a PRESUMPTIVE diagnosis of leptospirosis and a

total score of 20-25 suggests a POSSIBLE but unconfirmed diagnosis.

The Faine's criteria, with a number of modifications, had been used in the past to aid in the diagnosis of leptospirosis among adults. However due to the increasing and alarming incidence of the disease in our country, the need to come up with more precise and suitable criteria for its diagnosis among children is imperative. Not only does the disease have similar manifestations with other common pediatric illnesses, it can also cause severe complications like renal failure,^{5,6} meningitis,⁶ and pulmonary hemorrhage,⁷ and ultimately, it may lead to death.^{6,8,9}

Aside from the fact that only a handful of studies were done on leptospirosis in the pediatric population, this study will be the first to validate the modified Faine's criteria in the diagnosis of the disease in children.

This study aims to determine the sensitivity, specificity, positive and negative predictive values and likelihood ratios of positive and negative tests of the Modified Faine's criteria (Parts A and B) proposed by Brato in the diagnosis of leptospirosis in children using the microscopic agglutination test as gold standard. It also aims to determine which clinical criteria are relevant in the diagnosis of leptospirosis in Filipino children.

METHODOLOGY

Study Design

This diagnostic, validity study was conducted at the Philippine General Hospital (PGH) and was approved by the Ethics Review Board. Its objective is to determine the validity of the Modified Faine's criteria as proposed by Brato. The modified criteria included abdominal pain and the revision in the scoring by adding 10 points when three out of the four criteria (i.e. abdominal pain, conjunctival suffusion, meningism and muscle pain) were present; this is different from the WHO Faine's criteria which included muscle pain, conjunctival suffusion and meningism. These revisions were recommended because upon

validation of the WHO Faine's criteria, it proved to be inadequate to make a presumptive diagnosis of leptospirosis. Shivakumar of India and Roman had similar findings upon validation of the WHO Faine's criteria using a larger sample size. Moreover, this Modified Faine's criteria was used by several institutions during the outbreak.

Study Population

This study included all pediatric patients 18 years old and below, who were admitted in PGH between September 2009 to December 2010 and who satisfied the presumptive and suggestive criteria in the diagnosis of leptospirosis based on the Modified Faine's criteria proposed by Brato. The diagnosis of Leptospirosis was based on significant contact with flood water and had the following manifestations: fever, headache, abdominal pain or diarrhea, conjunctival suffusion, meningism, muscle pains especially calf pain, jaundice and albuminuria. Patients who had single MAT results were excluded.

The list of patients was gathered from the logbooks of the Pediatric Emergency Room (PER), pediatric wards and medical records section (using ICD 10). Data on demographic characteristics, symptom reporting, clinical presentation, contact with contaminated environment, scoring based on the Modified Faine's criteria, physical examination findings, clinical outcome, laboratory work-ups (CBC, blood chemistry, urinalysis) and paired MAT titer were also obtained.

Using the sample size formula for estimating sensitivity and specificity, the minimum sample size required is 262 in order to achieve a confidence level of 90%. Fifty percent sensitivity and 43% specificity were used in the computation based on a multicenter local study done in adults by Roman et al.¹⁰ Meanwhile, a 26% prevalence of leptospirosis was used in this computation based on the study of Borja entitled "PCHRD-DOST Final Report of the Burden of Disease of Leptospirosis". Total enumeration was done to

meet the sample size requirement due to insufficient data.

However, this study was carried out because of the increase in the number of cases of leptospirosis admitted after typhoon Ondoy. The information gathered from this study may still be useful in making recommendations regarding early diagnosis of leptospirosis in children.

Laboratory Technique

Microscopic Agglutination Test

A licensed medical technologist from the laboratory of the University of the Philippines Manila College of Public Health performed the MAT. Serial dilution of serum kept in contact with an equal volume of a well-grown suspension of leptospores at a certain temperature and for a certain period of time was read microscopically by estimating 50% agglutination as the endpoint titer of the reaction mixture.¹¹ A panel of 17 *Leptospira* serovars (18 strains) was used as antigens in MAT. MAT was done at doubling dilutions starting from a titer of 1 in 50. Positive samples were titrated up to a titer of 1 in 51,200. Titers of 1:400 and above were read as positive. MAT was done on all acute and convalescent serum samples collected two to three weeks apart from suspected cases.

A *Positive Modified Faine's Criteria* is a score of ≥ 26 in part A, or parts A and B of the Modified Faine's criteria while a *Negative Modified Faine's Criteria* is a score of < 26 in part A, or parts A and B of the Modified Faine's criteria.

A *Positive MAT* was defined as a fourfold or greater rise in MAT titers between acute and convalescent serum specimens obtained at least 2 weeks apart.¹²

Accordingly, the following modification was applied using as reference a previous local study by Roman.¹⁰ An additional 10 points was added to the total points in the Modified Faine's criteria when only conjunctival suffusion and muscle pain were seen in the patient. This, then, will be labeled as "Pediatric Locally

Modified Faine's Criteria" and validated with MAT.

Modified Faine's Criteria

Part A: Clinical Data	
Headache of sudden onset	2 points
Fever	2 points
If fever, temp 39C or more	2 points
Abdominal pain or diarrhea*	4 points
Conjunctival suffusion (bilateral)*	4 points
Meningism*	4 points
Muscle pains (esp calf muscles)*	4 points
*Are 3 out of 4 features present together?	10 points
Jaundice	1 point
Albuminuria or Nitrogen retention	2 points
Part B: Epidemiological Factors	
Contact with animals at home, work, leisure or in travel, or contact with known (or possibly) contaminated water	10 points
Part C: Bacteriological Laboratory Findings	
Isolation of Leptospire in culture--→diagnosis certain	
Positive Serology- Leptospirosis endemic	
Single positive, low titer	2 points
Single positive, high titer	10 points
Paired sera, rising titer	25 points
Positive Serology- Leptospirosis NOT endemic	
Single positive, low titer	5 points
Single positive, high titer	15 points
Paired sera, rising titer	25 points

Presumptive diagnosis of leptospirosis= 26 or more from Part A, or Parts A and B OR 25 or more from the total of Part A, B and C

Suggestive but Unconfirmed Diagnosis= a score between 20 and 25

Data Analysis

Data were encoded and analyses were carried out using Statistical Package for Social Sciences version 10 for Windows. Descriptive statistics were generated for all variables.

Calculations for sensitivity, specificity, positive and negative predictive values, and likelihood ratios of positive and negative tests were computed from the 2x2 table. Fisher's exact test was used to compare the proportions in the two groups (positive and negative MAT). A significance level of 0.05 was used in testing the hypotheses of the study.

RESULTS

Thirty-three charts satisfied the presumptive and suggestive criteria in the diagnosis of leptospirosis based on the Modified Faine's criteria; however, only 20 of these had paired MAT titers. Mean age was 13 years old (SD±4) the youngest patient was seven years old while the oldest was 18 years old. The male-to-female ratio was 2:1. The most common symptoms were fever, headache, abdominal pain, muscle pain and conjunctival suffusion (Table 1). Among those who were MAT positive, muscle pain and conjunctival suffusion were the most common symptoms reported while headache and abdominal pain were most common among those who were MAT negative. However, there was no statistical difference in the frequency of the symptoms among the two groups (Table 2). The Modified Faine's criteria had a sensitivity of 60%, specificity of 73%, positive predictive value of 43%, negative predictive value of 85%, positive likelihood ratio of 2 and negative likelihood ratio of 0.4 in diagnosing leptospirosis in children (Table 3).

In this study, no patient presented with meningism and the most common symptoms among the MAT positive cases were fever, muscle pain and conjunctival suffusion. Among these symptoms, muscle pain and conjunctival suffusion were observed to be most characteristic of leptospirosis.^{4,13,14} It is based on these observations that this modification—adding ten points if the patient had conjunctival suffusion and muscle pain—was done in order to come up with a criteria more appropriate in the diagnosis of leptospirosis in children.

Table 1. Distribution of cases according to the factors found in Parts A (symptoms) and B (epidemiologic factors) in the Modified Faine's criteria.

Factor	Number	Percent
Part A		
Headache of sudden onset	15	75
Fever	20	100
Fever >39 C	20	100
Abdominal pain or diarrhea	15	75
Conjunctival suffusion	12	60
Meningism	0	0
Muscle pains	15	75
Jaundice	3	15
Albuminuria or Nitrogen retention	5	25
Part B		
Contact with animals or contaminated water	20	100

When the "Pediatric Locally Modified Faine's Criteria" was used in this study, increase in the following were noted: sensitivity from 60% to 80%; positive predictive value from 43% to 50%; negative predictive value from 85% to 92%; positive likelihood ratio from 2 to 3; and negative likelihood ratio from 0.4 to 0.3. (Tables 4& 5)

Table 2. Comparison of Clinical Criteria found in Part A in the Modified Faine's criteria among MAT positive and MAT negative cases

Signs and Symptoms	MAT positive (n=5)	MAT negative (n=15)	p value
Headache of sudden onset	3 (60%)	12 (80%)	0.560
Fever	5 (100%)	15 (100%)	NA
Fever >39 C	5 (100%)	15 (100%)	NA
Abdominal pain or diarrhea	3 (60%)	12 (80%)	0.560
Conjunctival suffusion	4 (80%)	8 (53%)	0.603
Meningism	0	0	NA
Muscle pains	5 (100%)	10 (67%)	0.266
Jaundice	1 (20%)	2 (13%)	1.000
Albuminuria or Nitrogen retention	3 (60%)	2 (13%)	0.073

Table 3. Validation of the Modified Faine's criteria (Part A or Parts A and B) with MAT

Modified Faine's criteria	Positive MAT	Negative MAT	Total
Positive	3	4	7
Negative	2	11	13
Total	5	15	20

Table 4. Validation of the Pediatric Locally Modified Faine's criteria (Part A or Parts A and B) using MAT

Pediatric Locally Modified Criteria	Positive MAT	Negative MAT	Total
Positive	4	4	8
Negative	1	11	12
Total	5	15	20

Table 5. Summary of the Measures of Accuracy in the Modified Faine's Criteria and Pediatric Locally Modified Criteria

Measures of Accuracy	Modified Faine's Criteria	Pediatric Locally Modified Criteria
Sensitivity	60%	80%
Specificity	73%	73%
Positive Predictive Value	43	50%
Negative Predictive Value	85	92%
Positive Likelihood Ratio	2	3
Negative Likelihood Ratio	0.4	0.3

DISCUSSION

Leptospirosis, which is one of the emerging infectious diseases worldwide, is endemic in the Philippines, a tropical country. In 2009, when typhoon Ondoy hit the country, the number of consults from both pediatric and adult patients increased in several hospitals.

Males, as cited by different local studies in children,^{5,7,8} were still predominantly affected

by leptospirosis. The serovars commonly isolated were *L.patoc* (100%), *L. poi* (80%), *L. manilae* (60%) and *L. hardjo* (60%) in order of frequency. This is in contrast to the study done in 1977 where *L. pyrogenes* and *L. manilae* were the common serovars.⁸

Severe complications of leptospirosis commonly seen in the adult population like meningitis, cardiac arrhythmias, severe pulmonary hemorrhage and Weil's syndrome were not seen in this study. However, three of the confirmed leptospirosis cases had non-oliguric renal failure but did not require dialysis. Hemorrhagic diathesis had been attributed to depletion of serum prothrombin or thrombocytopenia or of both.¹⁵ In this study, two had blood-stained sputum but the only derangement found was in the serum partial thromboplastin time.

A local study done by Brato, et al, in 1998 validated the WHO Faine's criteria (Parts A and B) in the diagnosis of leptospirosis using MAT as gold standard. This was done in 53 adult patients and it reported a sensitivity of 33%, a specificity of 65%, a positive predictive value of 67%, and a negative predictive value of 31%. Said study cited the small sample size and inability to collect the sera for the second titer on the recommended weeks as reasons for the low values obtained. They recommended modification of the WHO Faine's criteria by adding abdominal pain or diarrhea in the clinical features (part A) with a score of four.¹⁶

After this validation study, a number of other studies modified the WHO Faine's criteria. In India in 2004, Shivakumar, et al, did a prospective study on 150 patients suspected with leptospirosis by utilizing the modified Faine's criteria (modified to suit people in India) and they suggested the following modifications: (1) incorporation of factors such as rainfall and contact with contaminated environment to Part B; and (2) inclusion of Enzyme-linked Immunosorbent Assay (ELISA) and Slide agglutination Tests (SAT) in the diagnosis. They reported that the standard WHO Faine's criteria had a sensitivity of 41.9%, a specificity of 84.9%

and a positive predictive value of 41.9%. In contrast, modified Faine's criteria had a sensitivity of 58%, a specificity of 97.4% and a positive predictive value of 85.7%. This study emphasized the importance of simple diagnostic tests (ELISA and SAT) in the diagnosis of milder forms of leptospirosis.¹⁷

A more recent multicenter local study done by Roman et al in 2009 with 222 adult patients also validated the Modified Faine's Criteria proposed by Shivakumar of India using MAT and/or culture which showed sensitivity of 50%, specificity of 43%, positive predictive value of 4% and negative predictive value of 95%. They also proposed a different scoring system in the clinical part and a different cut-off for the MAT titer to increase sensitivity of the Modified Faine's criteria in the diagnosis of leptospirosis.¹⁰

Using Brato's Modified Faine's criteria, it was noted that the sensitivity and PPV were low, similar to the results seen in previous studies. These values were obtained even with the addition of abdominal pain in its clinical part. A positive predictive value of 43% would indicate that less than half of those who had a positive Modified Faine's criteria will turn out to have leptospirosis. Furthermore, a low positive likelihood ratio of 2 would indicate that a positive test result will not change the likelihood of leptospirosis being present. However, the Modified Faine's criteria was shown to have a moderately good negative predictive value and in this pediatric population, 85% of those with a negative Modified Faine's criteria will correctly turn out not to have leptospirosis; this is supported by a negative likelihood ratio of 0.4.

It has been proven that leptospirosis is difficult to distinguish from a number of other diseases on clinical grounds, especially that the clinical manifestations vary in terms of severity, from mild to rapidly fatal. Such being the case, a reference tool to diagnose the disease in its early course should be sensitive and should have a high PPV to be able to give an accurate

diagnosis and thus deliver prompt and specific treatment for a favorable clinical outcome.

The Pediatric Locally Modified Criteria, with its revised scoring system, yielded better results in terms of the sensitivity and negative predictive value. However, the positive predictive value and positive likelihood ratio remained to be low and as such, this new criteria still cannot be used as a diagnostic tool in the early diagnosis of leptospirosis in children.

Alimitation of this study is the small sample size. This is due to the few confirmed cases of leptospirosis in PGH where they only range from three to six in number per year. Also, it was difficult to obtain the second blood sample for the convalescent sera of the MAT since most of the patients did not follow up.

CONCLUSIONS

Using the paired MAT as gold standard, the Modified Faine's criteria was shown to be an insufficient reference in the early diagnosis of leptospirosis in children. Modifying the clinical criteria resulted in higher sensitivity and NPV. It is recommended that this "Pediatric Locally Modified Criteria", which showed better results, be validated in a larger sample of pediatric patients, preferably in different centers in the Philippines.

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