Original article

Clinical profile and role of serology in pediatric acute febrile illness: Experience from a tertiary care hospital in South India

Vaishnavi Kavirayani^a, Mridula Madiyal^{b,*}, Shrikiran Aroor^c, Sonakshi Chhabra^a

^a Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka - 576104, India

^b Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka - 576104, India

^c Department of Pediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka - 576104, India

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ABSTRACT

Problem addressed: Acute febrile illness (AFI) is a diagnostic challenge for the laboratory and clinicians. Serological diagnosis plays a major role in diagnosis of AFI. The data regarding pediatric AFI is limited. The present study was conducted to evaluate the clinical spectrum of acute febrile illness (AFI) in pediatric patients, along with the role of various diagnostic modalities.

Method: It was a retrospective observational study. The clinical and laboratory data for the pediatric AFI cases were collected and analyzed for percentage of etiologies and role of serological assays.

Results: Out of 214 cases studied, 57.9% were males, and 42.1% were females. Majority children were <10 years. Fever alone was seen in 36% of cases. The other common presentations were upper respiratory tract illness and gastroenteritis. Mean duration of fever was six days. Leukocytosis was seen in 36.4% of cases. Increased AST and ALT was noted in 48.7% and 39.5% of cases. Serological tests gave a positive result in 14.9% of cases. Most common disease diagnosed was Dengue (10/94 samples tested). Percentage positivity for different immunoassays was 31.8% for Hepatitis A- ELISA, 9% for Hepatitis E ELISA, 2.9% for Scrub typhus ELISA, 5% for Leptospirosis ELISA, 10.6% for Dengue ELISA. Febrile agglutination tests for Brucellosis, Typhoid and Rickettsial diseases showed positivity of 3.9%, 1.7% and 7.1% respectively. Clinical recovery was documented in 96.5% of cases with no significant association with serological positivity.

Conclusion: Serology is important in diagnostic work-up of AFI in children. However, the approach towards diagnosis needs to be syndromic with other modalities depending on the clinical suspicion.

1. Introduction

Fever is known to be the most common symptom in any systemic illness and has a huge role to play in morbidity. Every year, different parts of the world are affected by seasonal fevers.^{1,2}

Acute febrile illness (AFI) is classically defined as fever <2 weeks, rapid onset, caused by diverse pathogens without any system or organ-specific aetiology. Due to overlapping clinical presentation and limited microbiological services available in many low resource areas, very few patients receive an accurate and specific diagnosis at the community level, the relative importance of various causes of fever remains unknown.

Fever in children signifies systemic inflammation, typically in

response to a viral, bacterial, parasitic, or less commonly, a non-infectious aetiology. Geographic settings and patients' ages can help point to the appropriate diagnosis and treatment if local epidemiology is well understood. AFI can be potentially fatal if the aetiology is not recognised and if not appropriately treated early.

Mostly seen in the tropical and subtropical regions, AFI has the highest incidence in childhood-majority between 4 and 5 years of age. In tropical countries like India, the most common reasons for AFI are Dengue, Malaria, Typhoid fever, Leptospirosis and Rickettsial infection. Acute respiratory infections and viral exanthematous fevers also affect children significantly. Population density and urbanisation may contribute to the emergence and re-emergence of some of these diseases in tropical regions.³

* Corresponding author. Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka - 576104, India.

E-mail addresses: vaishnavi.kavirayani@learner.manipal.edu (V. Kavirayani), mridula.m@manipal.edu (M. Madiyal), shrikiran.a@manipal.edu (S. Aroor), Sonakshi.chhabra29@gmail.com (S. Chhabra).

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In tropical countries, malaria is frequently the cause of AFI followed by other non-malarial reasons.^{4–6} Viral respiratory tract infections are more seen in middle east countries.⁷

The most critical issue for primary-care physicians is to focus on the fever's aetiology and to rule out serious diseases. Distinguishing a patient with viral illness from one with bacterial infection is essential as there may be considerable overlap in the clinical appearance.

Due to uncertainties and shortage of data in this field, clinical decision-making often gets compromised. There is deficiency of data in pediatric age group regarding AFI. Understanding the pattern of AFI and decoding various clinical and diagnostic clues will help to identify the aetiology, thereby expediting the treatment process. In this context, we have conducted a cross-sectional retrospective study to determine the prevalence of local infectious diseases causing AFI in our geographical area. The objectives were to evaluate the microbiological aetiology of acute febrile illness (AFI) in pediatric patients using serological and bacterial cultures and to understand the clinical profile of acute febrile illness in pediatric patients.

2. Materials and methods

A cross-sectional retrospective 6-month study was conducted in a tertiary health-care hospital of South India (Karnataka) from January 2018 to June 2018.

2.1. Search strategy

The research included pediatric patients of age group <18 years, admitted to the hospital with febrile illness between the 6-month period of study. The study was approved by the institutional ethics board. Ethic clearance number: IEC 505-2019.

Hospital numbers of pediatric patients were collected and evaluated for AFI from microbiology laboratory records. Clinical profile of each patient, which includes history of illness, symptoms, signs, investigations undertaken and respective management was documented from hospital records as per the proforma.

2.2. Information and data extraction

The proforma constituted general information of the patient (age, gender, residence, date of admission, date of discharge, etc.), associated risk factors (like undernutrition, immunosuppression, intake of poultry/meat, contact with domestic animals, history of insect bite, etc.), associated organ systems that were particularly involved, clinical symptoms and signs – with duration and detailed description of each and laboratory diagnosis, which involved biochemical, hematological, microbiological, serological and statistical analysis.

2.3. Laboratory diagnosis

The biochemical and hematological parameters mainly included liver function markers, blood indices and inflammatory markers. The data collected also included microbiological work up such as immunoassay, molecular tests, and bacterial cultures. The serological investigations used for analysis were commercial Enzyme Linked Immunosorbent assays (ELISA) for the detection of IgM antibodies of the various infectious etiologies for AFI. The list included IgM ELISA result for Scrub typhus, Leptospirosis, Hepatitis A, Hepatitis E and Dengue. We also collected results of febrile agglutination tests as Widal test, Weil Felix test and Standard agglutination test for Brucellosis.

2.4. Statistical analysis

The statistical analysis mainly involved calculation of percentages. Categorical variables have been expressed in percentages and continuous variables in median and interquartile range. Chi-square test was

used to find the association between categorical variables. The result was considered statistically significant when p-value obtained was <0.05.

3. Results

357 pediatric AFI patients were evaluated, who visited the hospital between January 2018 to June 2018. The study team could retrieve clinical data for 214 cases. Out of 214 patients, 124 (57.9%) were males, and 90 (42.1%) were females. Nearly 34.1% were <5 years of age, 33.2% belonged to 6–10 years of age, 25.2% to 11–15 years of age and the least, 7.5% to age group >15 years [Table 1]. The mean affected age was 8.23 ± 4.08 years and average duration of fever at the time of presentation was six days.

All the patients showed fever as the primary symptom. Seventy-seven cases accounting for 36% presented with fever alone, whereas other patients had symptoms persistent to various organ systems. Upper respiratory tract and gastrointestinal tracts are the frequently involved systems with 19.6% and 18.2% respectively. Twenty-five cases (11.6%) presented with exanthematous fever. Documentation of undernourishment was noted in 50% of the patients, whereas, 19% were immunosuppressed, 1.7% of the patients consumed raw milk, and were in recent

Table 1
Demographic Characteristics in pediatric patients suffering from AFI.

Demographic characteristic	Details/subgroups	Number	Percentage
Age	<5 Years	73	34.1%
	6–10 Years	71	33.2%
	11–15 Years	54	25.2%
	>15 Years	16	7.5%
Duration of fever	<7 days	139	65%
	8–14 days	36	17%
	15–21 days	21	10%
	>21 days	18	8%
Vaccination Status	Age appropriate	190	89%
	Incomplete	9	4%
	Unvaccinated	6	3%
	No information/history	9	4%
Risk factors	Undernutrition	107	50%
	Immunosuppression	40	19%
	Raw milk consumption	4	1.7%
	Contact with domestic animals	4	1.7%
	Insect bite	22	10.3%
	Immunosuppression + Raw milk	4	1.7%
	Outside food consumption	7	3.4%
	Undernutrition + Contact with domestic animals	4	1.7%
	Undernutrition + Immunosuppression	22	10.3%
	Past history of surgery	14	6.5%
	Chronic illness	15	7%
	Recent travel	6	2.8%
Clinical symptoms	Cough	82	38.3%
	Abdominal pain	49	28.8%
	Headache	36	16.8%
	Vomiting	82	38.3%
	Diarrhoea	15	7%
	Breathlessness	7	3.2%
	Burning micturition	3	1.4%
Clinical signs	Anaemia	55	25.7%
	Jaundice	16	7.47%
	Neck rigidity	2	0.93%
	Hepatomegaly	70	33.1%
	Splenomegaly	19	8.87%
	Crepitations	7	3.27%
	Rash	30	14.4%

contact with domestic animals, 10.3% gave a history of recent insect bite and 3.4% of the patients consumed outside food.

Only 2.8% of the patients gave a positive history of recent travel. 88.8% of the children were vaccinated appropriately according to their age, whereas remaining were not vaccinated or had not completed their vaccination dose.

Other than fever, cough and vomiting were the most common symptoms accounting to 38.2% (82/214) of children. 22.8% and 16.8% of children experienced pain abdomen and headache, respectively. Most frequent clinical signs were hepatomegaly (33.1%), anaemia (25.7%) and rash (14.4%).

8.4% of the patients had thrombocytopenia, 18.9% had leukopenia, and 36.4% tested leukocytosis. 39.5% and 48.7% of patients had increased ALT and AST, respectively. 27.6% of children also tested hypoalbuminemia. Mean PT was 13.28s, while mean aPTT was 34.26s in the study population [Table 2] [Fig. 1].

3.1. Serological work-up

Serological tests gave a positive result in 14.9% cases (32/214). The most common serologically confirmed diagnosis was Dengue in 10 out of 94 tested samples (10.6%) whereas percentage positivity was high in IgM ELISA for HAV (31.8%, 7/22). Four patients each tested positive for IgM ELISA for Leptospirosis and Scrub typhus out of 79 and 135 tested, respectively. Most common serological investigation performed was IgM ELISA for Scrub typhus followed by Widal test [Fig. 2].

There were three cases with positive blood culture and one patient with a positive urine culture. The blood cultures isolated Methicillin-resistant *Staphylococcus aureus*.

Duration of fever did not show statistical association with serological test positivity. Among the serological tests, positivity for IgM ELISA for HAV had significant statistical association with pain abdomen ($p = 0.008$) and hepatomegaly ($p = 0.01$). Widal positivity was significantly associated with pain abdomen and diarrhoea ($p = 0.02$ and $p = 0.04$). Positive history of breathlessness was associated with IgM ELISA for Scrub typhus with a p value of 0.04. Dengue serology was significantly associated with hepatomegaly ($p = 0.001$). Other clinical findings as anemia, clubbing, splenomegaly failed to statistically show association with serological positivity.

3.2. Clinical outcome

Clinical recovery was seen in 207 cases accounting for a recovery rate of 96.5%. Two cases were discharged against medical advice and one child expired due to sepsis. We could not get outcome result for two cases. Serologically positive Dengue cases showed a recovery of 90%. For the other serological tests, all positive cases showed recovery. There was no statistical significance established between test positivity and clinical outcome.

Table 2
Statistics from laboratory parameters.

Laboratory parameter	Median	Inter quartile range
Haemoglobin (g/dl)	11.8	(10.5, 11.8)
Total WBC (cells/mm ³)	8750	(5,500, 13,675)
Platelets (cells/mm ³)	2,35,000	(1,39,000, 3,29,750)
Total bilirubin (mg/dl)	0.41	(0.23, 1.20)
Conjugated bilirubin (mg/dl)	0.16	(0.11, 0.51)
Unconjugated bilirubin (mg/dl)	0.22	(0.11, 0.41)
AST (u/L)	43	(32, 102)
ALT (u/L)	26	(15.25, 74.75)
ALP (IU/L)	163.5	(125.25, 227.50)
Serum albumin (g/dl)	3.8	(3.3, 4.8)

4. Discussion

The study is one of only a few in the world that focusses solely on pediatric patients. It characterizes children presenting to tertiary healthcare with AFI in South India. A total 214 pediatric patients with AFI symptoms could be evaluated as part of the study.

Most of our study population consisted of children <5 years of age (34.1%). Common organ systems involved in our study were upper respiratory tract and gastrointestinal tract. However, in 64% of the patients, fever was the only presenting symptom. According to a survey by Kheng Chheng et al.,⁸ Lower respiratory tract infection (LRTI) and gastroenteritis were the most common findings. Majority of the patients presented with cough and vomiting, followed by pain abdomen and headache. Most patients showed hepatomegaly, followed by anaemia and rash. Hepatomegaly also was significantly associated with positivity rate of IgM ELISA for HAV. Anaemia observed in many cases might be due to its association with acute infections. In viral infections, it might be due to inhibition of medullary erythropoiesis.⁹ In children, however, the degree of anaemia depends on whether the child has concomitant haemolytic anaemia or is healthy-in which case, the drop in haemoglobin is, slow and there is the rapid recovery of RBCs in one to two weeks. According to a study by Marcos et al.,¹⁰ children aged six months-5 years, are particularly prone to iron deficiency anaemia.

The study also showed thrombocytopenia in 8.4% and leukocytosis in 36.4% of patients. Febrile thrombocytopenia is seen in Malaria, Dengue and Enteric fever, which is relevant to the obtained findings. Leukocytosis, on the other hand, is almost always present along with acute infections. Liver function tests reveal elevated liver enzymes like ALT (40%), AST (49%) and ALP (62%). Most of the causative agents of AFI are known to affect liver functions.

Dengue was the common infectious aetiology followed by Hepatitis A and Scrub typhus as per serology. The review by Iroh Tam PY et al.,¹¹ Leptospirosis, Dengue, Rickettsiosis and Typhoid are the common diseases in the Asian region.

In a study conducted by Yogendra Pandurang Shelke et al.,¹² Scrub typhus was the predominant (47%) infection among the AFI cases, followed by Dengue 17.40% and malaria in 12% cases. A study conducted by Jung et al.¹³ showed 56.6%, and a study conducted by Sinha et al.¹⁴ did not show scrub typhus patients with eschar among 42 positive cases of scrub typhus which was included in their research. Our study results were like the study conducted by Solanke et al.,¹⁵ in which Dengue positivity was 28.4%. Along with serology, they had also detected Dengue by PCR. In India, dengue positivity ranged between 8% and 71% among AFI cases. The studies conducted in Tamil Nadu, Dehradun, showed Dengue is a prime cause of AFI cases. We reported Leptospirosis in 2% of AFI cases, like study carried out by Joshi et al. and Yogendra Pandurang Shelke et al.^{4,12}

The clinical recovery was found to be 96.5% in present study. In a study from Africa conducted by Kabore et al.,¹⁶ 85.1% clinically recovered, 9.2% were referred to other centres, 1.5% were sent home against medical advice and 4.2% died. In another study conducted by Chheng et al.⁸ the median duration between acute and discharge samples was 4 days and a mortality of 5.6% was observed, mostly in children with comorbidities. In a Singapore based study¹⁷ the recovery rate was at an average of 1.18 cases per person-week. Also, those with low WBC count had slower recovery as compared to those with normal or higher WBC count.

Our study reinforces that most of the clinical management relies on assessing clinical signs and symptoms compared to microbiological investigations. It also shows the necessity to have a diagnostic algorithm that includes all testing modalities depending on illness and presentation time. The study also gives an idea about the crucial aspects to be necessarily considered for the definitive diagnosis. We also agree that the study had shortcomings in terms of sample size. We could not establish a statistical association between duration of fever and test positivity. This would have increased the strength of serological

Fig. 1. Laboratory parameters of pediatric patients suffering from AFI.

Fig. 2. Serological test results in pediatric patients suffering from AFI.

evidence in diagnosis of pediatric AFI.

A larger cohort would have helped to look at the diagnostic role of each of the serological assays used. We also could have compared cases with a definitive diagnosis with those without a laboratory-confirmed diagnosis. However, due to the smaller sample and retrospective study design, statistical outcome could not be strong in the study.

5. Conclusion

The diagnosis and management of Acute Febrile Illness continues to pose as a concern to the physician. Even with all the newer diagnostic

facilities, AFI remains a challenge for clinical decision making. The limited number of studies conducted on pediatric patients with AFI makes it difficult to compare and contrast with various aetiologies, diagnostic modalities, treatment measures and post discharge recovery rates across the world. Overlapping clinical signs and symptoms and cross-reacting results of the serological tests are the main reasons for the same. Various diagnostic tests available target molecules which signify different stages of disease progression. Serology has been an essential component of the diagnostic algorithm. Though popular view is to evaluate a test using the positivity that it offers in suspected case, it is also important look at the predictive power of negative result. Therefore,

it is essential to develop a comprehensive approach towards diagnosis of pediatric AFI, that takes into consideration stage of illness, probable aetiology and diagnostic probabilities of each test.

Ethics declaration

Ethical approval was taken from the Institutional Ethics Committee (IEC) of the affiliated institution. Institutional ethics approval number-IEC 505–2019.

Author contributions

VK: Conceptualization, data collection, formal analysis and writing original draft. **MM:** Conceptualization, methodology design, supervision, writing-review, and editing, supervision. **SC:** data collection and formal analysis, **SA:** Conceptualization methodology design, writing-review, and editing, supervision. All the authors discussed the results and approved the final manuscript.

Declaration of competing interest

Authors declare that they have no conflict of interest.

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