

Advanced serological tests – A paradigm shift in the diagnosis of febrile illnesses even with some atypical manifestations



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ABSTRACT

Background: Fever is a symptom, not a disease. It is the non-specific manifestation of several underlying illnesses. **Aims and Objectives:** The aims and objectives of this study were to determine the serological profile of patients with febrile illnesses, to study their different unusual presentations, and to study patients with coinfections with more than one type of disease. **Materials and Methods:** Blood samples from 15,000 febrile patients were collected during the study period of 6 months. Different serological tests were performed in our laboratory based on clinical suspicion and in a few patients, more than one type of tests were done. The unusual presentations of different diseases were studied. **Results:** Various percentages of male and female patients were seen suffering from different types of febrile illnesses. The different positive results out of total tests done for respective diseases were dengue (848/7708), vivax malaria (64/800), falciparum malaria (4/800), leptospirosis (95/798), scrub typhus (77/2433), enteric fever (75/1506), hepatitis B (143/9368), hepatitis C (11/9368), human immunodeficiency virus (HIV) (37/10900), systemic lupus erythematosus (5/158), acute renal failure (66/158), and syphilis (54/583). Different unusual presentations among patients with several diseases were noted, along with their percentages of occurrence. Coinfections among dengue and enteric fever (3%), mixed infection with *Plasmodium vivax* and *Plasmodium falciparum* (0.25%), scrub typhus and *Leptospira* (15.6%), hepatitis B and hepatitis C (0.649%), hepatitis B and HIV (5%), hepatitis C and HIV (8.33%), and syphilis and HIV (27.68%). **Conclusion:** Dengue fever was found to be the most common of all febrile illnesses. The different unusual presentations of those diseases should suggest an improved clinical suspicion and better diagnostic stewardship. Coinfection was most commonly seen among syphilis and HIV and these data must suggest to always looking for associated illnesses in a patient with a single diagnosis.

Key words: Serological test; Enzyme-linked immunosorbent assay; Dengue; Coinfection

INTRODUCTION

Fever is a symptom, not a disease. It is a non-specific manifestation of several underlying illnesses. Dengue and malaria occur due to the bite of infected *Aedes* and *Anopheles* mosquitoes, respectively. Dengue is a viral illness caused by dengue virus.¹ Malaria is caused by *Plasmodium* species, a parasite.² Leptospirosis is caused by indirect contact with water contaminated with infected animal urine. It is caused by a bacteria known as *Leptospira interrogans*.¹ Scrub

typhus is caused by the bite of trombiculid mite infected by *Orientia tsutsugamushi*.¹ Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV), and syphilis are transmitted by parenteral routes, sexually and by vertical transmission from mother to child.¹ Hepatitis B, Hepatitis C, and HIV are viral infections caused by Hepatitis B, Hepatitis C, and HIV, respectively.³ Syphilis is caused by *Treponema pallidum*, a bacteria.¹ Systemic lupus erythematosus (SLE) is an autoimmune condition.⁴ Acute rheumatic fever is caused by molecular mimicry in a patient with post-*Streptococcus*

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pyogenes sore throat infection.¹ Enteric fever is caused by infection with either *Salmonella* Typhi or *Salmonella* Paratyphi A, B, and C transmitted by feco-oral route.¹ Sometimes, coinfections with more than one pathogen can be seen in different cases. Sometimes, few unusual presentations can be seen in various diseased conditions which can be very misleading. There have been surprisingly lesser studies on serological profile of febrile illnesses with various diagnoses and study on atypical presentations of some commonly encountered illnesses and coinfection with two different types of infections in the same patient. Therefore, an observational study was undertaken to determine the serological profile of febrile illnesses and an account of various atypical presentations of those illnesses in the microbiology department, Calcutta National Medical College and Hospital, Kolkata.

Aims

To assess the usefulness of advanced Serological tests in diagnosis of several diseases presenting with fever and some unusual manifestations.

Objectives

To determine the serological profile of febrile illnesses amongst patients, to determine the demographic profile of the patients with different diagnosis, to determine the percentages of several atypical presentations in some commonly encountered diseases and to determine an account of occurrence of co-infections amongst patients.

MATERIALS AND METHODS

An observational study was conducted for 6 months from February 1, 2023, to August 1, 2023, in the department of microbiology at Calcutta National Medical College and Hospital, Kolkata, including 15000 febrile patients. The patients were selected by systematic random sampling. Various serological tests were performed in those febrile patients. Dengue NS1 and dengue immunoglobulin M (IgM) testing were done for suspected dengue patients, malaria parasite dual antigen (MPDA) kit testing done for malaria detection; *Leptospira* IgM enzyme-linked immunosorbent assay (ELISA) and scrub typhus IgM ELISA were done for the detection of *Leptospira* and scrub typhus; ELISA to detect HBsAg for hepatitis B and ELISA to detect anti-Hepatitis C virus (HCV) antibody for hepatitis C were used; HIV tri-dot test, an immunochromatographic test used to detect HIV using flow through assay principle; antinuclear antibody testing was used for the detection of SLE using latex agglutination principle; antistreptolysin O (ASO) titer testing was used as a screening test for the detection of acute rheumatic fever (titer >200 IU/mL was considered positive); rapid plasma regain testing was done to detect syphilis in

suspected patients; and widal test, a tube agglutination method was used to detect enteric fever (a titer >1: 160 for TH, TO, AH, and BH was considered positive). In some patients, more than one type of testing was done and in a few cases, coinfection with more than one infection was noted. Demographic profile of those patients was studied. Furthermore, the total urban and rural populations with respect to each type of infections were studied. Several atypical presentations of each type of disease were also studied and their percentages were calculated.

Inclusion criteria

All patients with febrile illnesses were included and they were selected by systematic random sampling during the study period.

Exclusion criteria

Patients with fever due to malignancy were excluded from the study.

Ethical clearance

For the present study, the ethical approval was taken from the Institutional Ethics Committee, Calcutta National Medical College and Hospital, Kolkata.

Statistical analysis

The data obtained were analyzed with the statistical tool R. The different percentages were calculated. Fisher's exact test/one-way Chi-square test was used for comparative analysis. The tests were evaluated at a confidence level of 95% and $P < 0.05$ was considered statistically significant.

RESULTS

During 6 months (February, 2023–August, 2023), samples were collected from 15,000 febrile patients selected by systematic random sampling, and an observation study was conducted. The age distribution was between 0 and 81 or above (Tables 1-5).

Table 1 shows age group and gender distributions amongst patients suffering from different diseases. The different age groups studied were 0–20 years, 21–40 years, 41–60 years, 61–80 years, and 81 and above.

Table 2 shows urban and rural distributions of various diseases detected by serological test. Urban populations were at risk of developing vector/rodent-borne diseases, transfusion or sexually transmitted diseases ($P < 0.05$), enteric fever, and SLE while rural populations were at risk of acute rheumatic fever ($P < 0.05$).

Table 3 shows total number of respective tests performed for each suspected disease and the total positive results.

Table 4 shows percentages of occurrence of several unusual manifestations in different types of diseases diagnosed in our study.

Table 1: Most common age group affected and the gender distribution among patients with different diseases			
Disease	The most common age group affected (years)	Male (%)	Female (%)
Dengue	21–40	60.8	39.1
Vivax malaria	21–40	72.5	27.5
Falciparum malaria	21–40	60	40
Leptospirosis	21–40	33.68	66.3
Scrub typhus	41–60	48.4	51.6
Hepatitis B	21–40	60	40
Hepatitis C	41–60	70	30
HIV	21–40	60	40
SLE	41–60	20	80
ARF	21–40	30	70
Syphilis	21–40	79.6	20.37
Enteric fever	0–20	55	45

HIV: Human immunodeficiency virus, SLE: Systemic lupus erythematosus, ARF: Acute renal failure

Table 2: Urban and rural distribution of various diseases		
Diseases	Urban (%)	Rural (%)
Vector/rodent-borne diseases (dengue, malaria, leptospirosis, and scrub typhus)	55	45
Transfusion-transmitted/sexually transmitted diseases (hepatitis B, hepatitis C, and HIV, syphilis)	60	40
Enteric fever	58	42
Acute rheumatic fever	35	65
Systemic lupus erythematosus	55	45

HIV: Human immunodeficiency virus

Table 3: Represents a total number of respective tests performed for each suspected disease and the total positive results			
Diseases	Test performed	Total no. of tests done	No. of tests with positive results with percentage positivity (%)
Dengue	Dengue NS1 and IgM	7708	848 (11)
Vivax malaria	MPDA	800*	64 (8)
Falciparum malaria	MPDA	800*	4 (0.5)
Leptospirosis	IgM ELISA	798	95 (11.9)
Scrub typhus	IgM ELISA	2433	77 (3.16)
Hepatitis B	HBsAg ELISA	9368	143 (1.526)
Hepatitis C	Anti-HCVAb ELISA	9368	11 (0.117)
HIV	ICT (Tri-Dot) test	10900	37 (0.339)
SLE	ANA test	158	5 (3.164)
ARF	ASO titer ^(a)	158	66 (41.77)
Syphilis	RPR test	583	54 (9.262)
Enteric fever	Widal test	1506	75 (4.98)

*A total of 800 MPDA tests were performed and looked for *Plasmodium vivax* and *Plasmodium falciparum* simultaneously. ^(a)Further ECG 12 leads and 2D echocardiography were performed for ASO titer test-positive patients. Modified Jone's criteria were used for final diagnosis. ⁵HIV: Human immunodeficiency virus, SLE: Systemic lupus erythematosus, ARF: Acute renal failure, MPDA: Malaria parasite dual antigen, IgM: Immunoglobulin M, ELISA: Enzyme-linked immunosorbent assay, RPR: Rapid plasma regain, ASO: Antistreptolysin O

Table 5 shows percentages of coinfections with varied infections amongst patients.

DISCUSSION

The present study was conducted in the department of microbiology, Calcutta National Medical College and Hospital, Kolkata, with objectives of determining serological profile of febrile illnesses among patients, to determine their demographic profile, to find the percentages of several atypical presentations in some commonly encountered diseases, to determine an account of occurrence of coinfections among patients. The key findings of our study were various percentages of male and female patients were seen suffering from different types of febrile illnesses. The different positive results out of total tests done for respective diseases were dengue (848/7708), vivax malaria (64/800), falciparum malaria (4/800), leptospirosis (95/798), scrub typhus (77/2433), enteric fever (75/1506), hepatitis B (143/9368), hepatitis C (11/9368), HIV (37/10900), SLE (5/158), ARF (66/158), and syphilis (54/583). Different unusual presentations among patients with several diseases were noted, along with their percentages of occurrence. Coinfections were seen amongst patients as following - dengue and enteric fever(3%), mixed infection with *P. vivax* and *P. falciparum* (0.25%), scrub typhus and leptospirosis (15.6%), Hepatitis B and Hepatitis C(0.649%), Hepatitis B and HIV(5%), Hepatitis C and HIV(8.33%) and syphilis and HIV(27.68%).

Discrepancies were seen in the age group and gender affected in this study as compared to other studies.¹ Here, the vector/rodent borne diseases were more prevalent in urban (55%) than rural (45%) population. Study by Colón-

Table 4: Percentages of occurrence of several unusual manifestations in different types of diseases diagnosed in our study

Disease	Unusual presentation	No. of patients affected out of total patients	Percentages of patients affected (%)	
1. Dengue	1. Bradycardia	30/848	3.537	
	2. Encephalitis	6/848	0.7	
	3. Confusion	20/848	2.358	
	4. Vertigo	12/848	1.41	
	5. Convulsion	10/848	1.179	
2. Vivax malaria	1. Drowsiness	6/64	9.375	
	2. Vertigo	2/64	3.125	
3. Falciparum malaria	1. Hematuria	1/4	25	
	2. Disorientation	2/4	50	
4. Leptospirosis	1. Oliguria	15/95	15.78	
	2. Melena	5/95	5.26	
5. Scrub typhus	1. Convulsion	10/77	12.98	
	2. Confusion	9/77	11.68	
6. Hepatitis B	1. Hyponatremia	30/143	20.97	
	2. Hematuria	20/143	13.98	
	3. Oliguria	8/143	5.594	
	4. Hemoptysis*	1/143	0.699	
	5. Petechiae	12/143	8.39	
7. Hepatitis C	1. Joint pain	4/11	36.36	
	2. Cryoglobulinemia**	1/11	9.09	
8. HIV	3. Hyperpigmentation of skin	8/37	21.62	
	4. Early CKD (chronic kidney disease)	7/37	18.9	
	5. Cardiomyopathy	12/37	32.4	
	9. SLE	1. Convulsion	1/5	20
		2. Hyperthyroidism	1/5	20
10. ARF	1. Chorea	5/66	7.57	
11. Syphilis	1. Tenosynovitis	2/54	3.7	
	2. SOB with palpitation	3/54	5.55	
12. Enteric fever	1. Pleural effusion	10/75	13.3	
	2. Joint pain	20/75	26.66	
	3. Pleuritic chest pain	8/75	10.66	

*This patient had hepatitis B-related vasculitis. **Serum protein electrophoresis for serum cryoglobulinemia testing was done from outside laboratory

Table 5: Percentages of coinfections among patients

Coinfections	Percentage of patients affected (%)
Dengue and Enteric fever	3
Mixed infections with <i>Plasmodium vivax</i> and <i>Plasmodium falciparum</i>	0.25
Scrub typhus and Leptospirosis	15.6
Hepatitis B and Hepatitis C	0.649
Hepatitis B and HIV	5
Hepatitis C and HIV	8.33
Syphilis and HIV	27.68

HIV: Human immunodeficiency virus

González et al., showed that urbanization trends may be associated with increased risk of vector/rodent borne infections.⁶ In our study, the various sexually transmitted infections were found to be more common in urban (60%) than rural (40%). Similar findings were shown by Verma et al.⁷ In our study, the percentages of enteric fever, acute rheumatic fever, and SLE were in urban (58%, 35%, and 55%) and in rural (42%, 65%, and 45%), respectively. Almost similar findings were shown by Breiman et al., and Sika-Paotonu et al.^{8,9} Dengue was found to be positive

in 11% of total tested patients during our study period. Study by Hati showed different results which may be due to difference in time frame between two studies.¹⁰ In the present study, the prevalence of vivax malaria, falciparum malaria, Hepatitis B, C, HIV, and syphilis corroborates while that of *Leptospira*, scrub typhus, enteric fever, SLE shows discrepancies with different studies.⁵ Discrepancy may be due to difference in demographic profile and geographic distributions. Here, 41.77% of patients had raised ASO titer and later diagnosis of acute rheumatic fever was confirmed by additional tests. As per an article, over 80% of patients with acute rheumatic fever have elevated ASO titer.¹¹ Hence, this suggests the importance of ASO titer as a screening test for acute rheumatic fever. In our study, several atypical manifestations were seen in dengue including – bradycardia (3.537%), encephalitis (0.7%), confusion (2.358%), vertigo (1.41%), and convulsion (1.179%). Some of these features are included under “expanded dengue syndrome.”¹ Similar results were shown by Mohan et al.¹² In the present study, atypical manifestations seen in vivax malaria were drowsiness (9.375%) and vertigo (3.125%), while in falciparum

malaria, hematuria (25%) and disorientation (50%) were seen. These manifestations are seen in many patients with malaria.² Here, atypical manifestations in leptospirosis seen were oliguria (15.78%) and melena (5.26%). Study by Ghasemian et al., showed oliguria in 31% and bleeding manifestations including severe gastrointestinal hemorrhage mainly in severe leptospirosis.¹³ In the present study, atypical manifestations of scrub typhus seen were convulsions (12.98%) and confusion (11.68%). Similar results were shown by Ramachandran and Gera.¹⁴ In our study, hepatitis B patients presented with few atypical manifestations including hyponatremia (20.97%), hematuria (13.98%), oliguria (5.594%), hemoptysis (0.699%), and petechiae (8.39%). In another study by Kappus and Sterling, the percentages of occurrence of glomerulonephritis (0.1–25%) as cause of hematuria with or without oliguria; polyarteritis nodosa, a rare vasculitis may lead to hemoptysis; hyponatremia in 1.2–21.6%, petechial rash may be seen in about 5% patients.¹⁵ In our study, atypical manifestations of hepatitis C seen were joint pains (36.36%) and cryoglobulinemia (9.09%). In another study by Kemmer and Sherman, cryoglobulin-related arthritis may occur in 10–30% of patients with HCV-related arthritis. Circulating mixed cryoglobulin complexes are detected as commonly as 40–50% patients in chronic HCV-infected patients.¹⁶ In our study, atypical manifestations of HIV seen were hyperpigmentation of skin (21.62%), early chronic kidney disease with raised creatinine (18.9%), and cardiomyopathy (32.4%). It has been seen that HIV infection leads to upregulation of IL-1, IL-6, and TNF-alpha which stimulates melanogenesis leading to increased production of melanin.⁵ Again patients with HIV are at risk for both acute kidney injury and chronic kidney disease as a result of nephrotoxic antiretroviral drugs, HIV-associated nephropathy, and immune complex disease of kidney.⁵ Dilated cardiomyopathy has been reported in HIV patients.⁵ In our study, atypical manifestations seen in SLE were convulsion (20%) and hyperthyroidism (20%). In another study by Iqbal et al., atypical manifestations seen included convulsions (6.2–58%) and hyperthyroidism (3–9%).¹⁷ Although rate of convulsion corroborates with this study, the rate of hyperthyroidism does not corroborate which may be due to difference in demographic pattern, climatic variations and lifestyle differences between two study populations. In the current study, the atypical manifestation seen in acute rheumatic fever was chorea which was found in 7.57% patients. Discrepancies have been noted with respect to several other studies. In our study, atypical manifestations seen in syphilis were tenosynovitis (3.7%) and shortness of breath with palpitation (5.55%). It has been seen that tenosynovitis is a rare manifestation of secondary syphilis.¹ Furthermore, signs of involvement of the heart and aorta in syphilis appear in the early stages

of the disease, suggesting the appearance of shortness of breath and palpitation.¹ In our study, several atypical manifestations of enteric fever seen were pleural effusion (13.3%), joint pain (26.66%), and pleuritic chest pain (10.66%). It has been seen that pneumonitis with pleural effusion, arthralgia, and pleuritic chest pain may occur as a result of pleural effusion.⁵ In our study, dengue and enteric fever coinfection were seen in 3% of patients. In another study by Sharma et al., dengue and enteric fever coinfection rates were 7.8%.¹⁸ This discrepancy may be due to variable microbial distributions in different geographical places. In our study, the *P. vivax* and *P. falciparum* mixed infection seen were 0.25% (2.85% of all malaria cases). Discrepancy has been noted in different geographical regions.¹ In our study, scrub typhus and *Leptospira* coinfection were seen in 15.6% of cases. Discrepancy has been noted in a study by Borkakoty et al., where scrub typhus and *Leptospira* coinfection was seen in 25% of cases.¹⁹ In our study, Hepatitis B and C coinfection was seen in 0.649% of patients. A study done in Western Europe revealed that the frequency of HBV-HCV coinfection was 0.68%.⁵ In our study, the HBV and HIV coinfection rate is 5%. As per another data, the HBV and HIV coinfection was found to be 5–10% in the United States.²⁰ In our study, the HCV and HIV coinfection was found to be 8.33%. In another data in United States, approximately 5% of adults with chronic Hepatitis C infection have coinfection with HIV.²⁰ Among persons living with HIV in the United States, an estimated 15–30% have HCV coinfection.²⁰ Hence, somewhat discrepancy is present which may be due to difference in geographical regions and individual risk factors. In our study, syphilis and HIV coinfection were seen in 27.68% of patients. In another study by Vergara-Ortega et al., HIV-syphilis coinfection was seen in 5.7% of cases.²¹ Hence, our study does not corroborate with this study which may be due to differences in geographical regions, demographic profile, and individual risk factors.

Strength of the study

- (1) An extensive study, different types of febrile illnesses were diagnosed by different serological tests.
- (2) Their demographic profile was studied.
- (3) Several atypical presentations of those illnesses were studied.
- (4) Coinfections with more than one type of infections were noted.

Limitations of the study

Although it was an extensive study, there were a few limitations – (1) several serological tests were performed for each type of disease, but molecular studies were not done, (2) further follow-up of their disease course was not done, (3) our study period was shorter.

CONCLUSION

Age groups 0–81 and above were included. Demographic profile revealed varied distributions of diseases among male and female patients with different age groups. Varied distributions of febrile illnesses were seen among patients from rural and urban populations. Dengue fever was found to be the most common of all febrile illnesses. The different unusual presentations of those diseases should suggest an improved clinical suspicion and better diagnostic stewardship. Coinfection was most commonly seen among syphilis and HIV and these data must suggest to always look for associated illnesses in a patient with a single diagnosis.

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Authors Contribution:

SG- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implement of the study protocol, data collection, data analysis, manuscript preparation, submission of article, concept, design of the study, statistical analysis and interpretation, editing and manuscript revision.

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