Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: https://www.ijmmtd.org/

Original Research Article

Pyrexia of unknown origin: A microbiological review of cases in pediatric population at a tertiary care hospital

Sneha S. Bowalekar[1,*], Vijitha Vijaykumar[1]

[1]*Dept. of Microbiology, Bai Jerbai Wadia Children's Hospital, Parel, Mumbai, Maharashtra, India*

ARTICLE INFO

Article history:
Received 15-03-2022
Accepted 07-04-2022
Available online 07-06-2022

Keywords:
Widal
Typhoid
Rickettsia
Brucella
Pediatric

ABSTRACT

Background: Pyrexia of unknown origin (PUO) was described as a persistent fever above 38.3°C (100°F) that evades diagnosis for at least 3 weeks, including 1 week of investigation in hospital. It may be caused by over numerous infectious, rheumatic/ inflammatory, malignant/neoplastic and miscellaneous disorders.
Materials and Methods: Blood specimen of 55 pediatric patients with fever of more than two weeks duration were tested for Typhoid, Rickettsial and Brucella infection serologically. Blood cultures of these patients were tested simultaneously.
Results: Positivity of Immunochromatographic testing for S. Typhi, Widal slide and tube agglutination test was 20%, 23.6% and 21.8% respectively. Titres of >=1:320 were observed in 4 (33.3%) of widal positive patients against H agglutinins. Positivity in Weil-Felix Tube Agglutination test was observed in 1(1.8%) patient against OX-K antigen, in 8 (14.5%) patients against OX-2 and in 6 (10.9%) against OX-19 antigen. Titre of 1:640 was observed in 1(1.82%) of patients against OX-2. One (1.8%) patient showed positive result in Brucella A/M Tube agglutination test.
Conclusion: Although serological investigations provide early and presumptive diagnosis of diseases, clinical features and epidemiological factors play an important role for initiation of treatment where facilities for culture and molecular testing are lacking or the results of the same are negative.

1. Introduction

Pyrexia of unknown origin (PUO) in children becomes apparent from different infectious causes in both developed and developing countries with limited amount of data from developing countries. Often the cause is an acute infection, which soon becomes evident and responds to treatment, or runs its course. In India, infectious diseases most commonly implicated in children with PUO are salmonellosis, tuberculosis, malaria, rickettsial diseases and atypical prolonged presentations of common viral diseases. Typhoid fever is still a cause of concern due to increasing antibiotic resistance. Its incidence is higher among children under five years of age as compared to adults because children either lack natural immunity or experience high levels of exposure to faecal pathogens. Rickettsial infections are one of the important causes of PUO, but still remain overlooked due to non-specific clinical presentations, low index of suspicion amongst clinicians, limited awareness, and limited diagnostic facilities in developing countries. The incidence of childhood brucellosis is usually under reported and it is ranging between 0.8-1.6%.[1]

2. Materials and Methods

The retrospective study was carried out in Department of Microbiology of a Tertiary Care Hospital, enrolling 55 children aged less than or equal to 18 years presenting

* *Corresponding author*.
E-mail address: sneha8503@gmail.com (S. S. Bowalekar).

https://doi.org/10.18231/j.ijmmtd.2022.025

to the outpatient department with history of fever and in whom no diagnosis could be made after basic investigations and cultures, from September 2018 to December 2018. Out of the numerous cases, children diagnosed with malaria, dengue, leptospirosis and urinary tract infections as cause of fever were excluded from the study. Children fulfilling the inclusion criteria for PUO had temperature of more than or equal to 38°C for more than 21 days without a specific clinical cause. The investigations performed for the diagnosis included Widal test, Weil-Felix test and Brucella test (by Slide and Tube Agglutination method), Salmonella IgM by Immunochromatography method and Blood Culture by BD Bactec 9050 and Bactec FX40 automated system.

3. Results

During the four months study period, 55 patients with fever, in whom no diagnosis could be made after the basic investigations, were followed up.

Table 1: Gender wise prevalence of PUO

Gender	Frequency	Percentage
Male	32	58.2
Female	23	41.8
Total	55	100

Table 2: Demographic characteristics (Age Range)

Age Range (In Years)	Frequency	Percentage
1-5	30	54.5
6-10	14	25.5
11-15	9	16.3
16-18	2	3.7
Total	55	100

Table 3: Results of S. Typhi IgM testing by Immunochromatography

	Frequency	Percentage
Positive	11	20
Negative	44	80
Total	55	100

Table 4: Widal slide test result for S. Typhi O and H agglutinin

	Frequency	Percentage
Positive	13	23.6
Negative	42	76.4
Total	55	100

Table 5: Widal tube test result for S. Typhi O and H agglutinin

	Frequency	Percentage
Positive	12	21.8
Negative	43	78.2
Total	55	100

Table 6: Percentage –wise titres obtained by widal tube agglutination

Titres	O	%	H	%
1:640	-	-	-	-
1:320	-	-	04	33.3
1:160	05	41.7	05	41.7
1:80	06	50	03	25
1:40	01	8.3	-	-
Total	12	100	12	100

Table 7: Results for weil-felix slide and tube agglutination test for rickettsial Infection

	Frequency			Percentage		
	OX-K	OX-2	OX-19	OX-K	OX-2	OX-19
Positive	01	08	06	1.8	14.5	10.9
Negative	54	47	49	98.2	85.5	89.1
Total	55	55	55	100	100	100

Table 8: Titres by weil-felix tube agglutination test for rickettsial infection.

Titre	OX-K	%	OX-2	%	OX-19	%
1:640	-	-	01	1.82	-	-
1:320	-		01	1.82	-	-
1:160	-		04	7.25	-	-
1:80 and Below	01	1.81	02	3.64	06	10.9
Total	01	1.81	08	14.54	06	10.9

Table 9: Results of brucella A/M slide and tube agglutination test

Result	Frequency	Percentage
Positive	01	1.8
Negative	54	98.2
Total	55	100

4. Discussion

Children with PUO should be evaluated with epidemiological data, contact history, previous medical history, fever pattern, detailed physical or screening tests to provide adequate information to establish a diagnosis.[2] Prevalence of enteric fever was significant (30.4%) in the age group of 0-21 years as per the study by Bharadwaj et al,[3] similar to the results obtained by Govindarajulu et al.[1] We got 20% positivity for Salmonella Typhi antibodies by immunochromatography assay, 23.6% positivity in widal slide agglutination test and 21.8% positivity by

widal tube agglutination assay. Five patients showed titres for >=160 for Salmonella Typhi O & H antigens, which were presumptively diagnosed and treated as Enteric fever. Definitive diagnosis of enteric fever requires isolation of S. Typhi or S. Paratyphi from blood of patient. However, sensitivity of blood culture is highest in the first week of illness and reduces with advancing illness. Conventionally, a positive widal test result implies demonstration of rising titres in blood or serum samples.[4]

Agglutinins to the somatic (TO) antigens develop later in the illness and decline slowly and variably in recovery, but those to flagellar antigens (TH) rise early and persist.[5] Somatic antigens are widely distributed, hence specificity for Salmonella might be lost. However, widal test is useful for cases in children, who have a low prevalence of pre-existing antibody.[6]

Serological assays are the simplest diagnostic tests to perform for rickettsial infections. The Weil–Felix test was the first to be used and involves antigens from three Proteus strains: P. vulgaris OX2, P. vulgaris OX19, and P. mirabilis OXK. Its use in the diagnosis of rickettsioses is based on serological cross reactions.[7] The test lacks sensitivity and specificity but has historically been used for laboratory diagnosis and provides evidence of newly encountered rickettsioses.

Interpretation of the Weil-Felix test requires knowledge of the disease course and corresponding immune response. A threshold for agglutinins that is considered "normal" is up to 1:40. It is especially seen with Proteus OXK suspensions, in which titers up to 1:160 have been observed in non-infected persons. A positive titer of 1:320 has been observed in 54% of healthy persons and 62% of persons with non-rickettsial infections, giving a low sensitivity with this threshold.[8]

In our study, only one patient (1.81%) had agglutinins against proteus OX-K antigens but the titre was below 1:80 hence was not held significant. Two patients (3.64%) showed similar titres against Proteus OX2 antigens whereas as many as six patients (10.9%) showed titres below 1:80 against Proteus OX-19 antigen. Four patients (7.25%) showed titres of 1:160 against Proteus OX2 antigens and one patient each showed titres of 1:320 and 1: 640 against the same antigen. However, these patients had no relevant clinical and epidemiological history, hence were not treated for typhus fever. The antibodies appear rapidly during the course of the illness, reach titre of upto 1:5000 by second week and decline rapidly during convalescence.[9]

Doxycycline is the drug of choice for the treatment of the rickettsioses. It was demonstrated that a single dose cured patients suffering from epidemic typhus and Mediterranean spotted fever. For other rickettsial diseases, a 7–14-day regimen is recommended. For children, doxycycline should also be used. It has been demonstrated that staining of teeth is unlikely to appear when fewer than five therapeutic courses of doxycycline are prescribed in childhood.[10]

Andriopoulos P. et al, conducted a study wherein 144 cases of brucellosis were identified and treated. Ninety-five percent of the patients had a serological titre >=1:160 with culture-proven brucellosis.[11] A study conducted by Alshaalan et al, reported positive brucella serology test result of >=1:160 using the standard agglutination test (SAT) for patients presenting with symptoms suggestive of brucellosis. For the purpose of screening and in the absence of clinical indicators of active brucellosis, a titre of 1:320 or higher is more specific for the presence of the disease.[11,12] Our study showed presence of one case (1.8%) with Brucella A/M tube agglutination titre of 1: 320.

5. Conclusion

Definitive dignosis of typhoid fever is made after obtaining growth of Salmonella Typhi or Salmonella Paratyphi A, B or C in blood cultures. Definitive diagnosis of Q fever could be made with growth of Brucella species in blood cultures but isolation may take as long as 14 days. Rickettsia PCR are diagnostic of rickettsial infections. Serological reactions for diagnosis of typhoid fever, rickettsial infections and brucellosis, though indicative of infection, cannot be completely relied on given their low specificity. Also, in the past few decades, new infectious disease etiologies have emerged as an important cause of PUO in developed countries, such as Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Human Immunodeficiency Virus (HIV), Psittacosis, Cat-Scratch disease or Bartonellosis. These are diseases capable of provoking high fever for weeks or months, or even years, without progressing and for which we might not have accurate methods of diagnosis. Definitive diagnosis of chronic infections, however requires culture or molecular testing.

6. Conflict of Interest

The authors declare no relevant conflicts of interest.

7. Source of Funding

None.

References

1. Govindarajalu S, Kalyanasundaram K, Pyarejan KS, Venkatasamy S. Clinical profile and etiological spectrum of fever of unknown origin in children aged 2 months to 12 years. *Int J Contemp Pediatr*. 2017;4(1):62–7. doi:10.18203/2349-3291.ijcp20164413.
2. Cunha BA. Fever of unknown origin. New York, USA: Informa Healthcare; 2007.
3. Bharadwaj BVG, Vazhavandal G, Uma A, Chitrarajalakshmi P. Prevalence of Enteric fever in patients with Pyrexia of Unknown Origin. *Asian J Biomed Pharmaceuticals Sci*. 2014;04(28):39–42.
4. Olopoenia LA, King AL. Widal agglutination test - 100 years later: still plagued by controversy. *Postgrad Med J*. 2000;76(892):80–4. doi:10.1136/pmj.76.892.80.
5. Shroeder SA. Interpretation of serologic tests for typhoid. *JAMA*. 1968;206(4):839–40.

6. Choo KE, Razif AR. Usefulness of the widal test in diagnosing childhood typhoid fever in endemic areas. *J Paediatr Child Health*. 1993;29(1):36–45. doi:10.1111/j.1440-1754.1993.tb00437.x.
7. Raoult D, Dasch GA. Immunoblot cross-reactions among Rickettsia, Proteus spp. and Legionella spp. in patients with Mediterranean spotted fever. *FEMS Immunol Med Microbiol*. 1995;11(1):13–21. doi:10.1111/j.1574-695X.1995.tb00073.x.
8. Kularatne SA, Gawarammana IB. Validity of the Weil-Felix test in the diagnosis of acute rickettsial infections in Sri Lanka. *Trans R Soc Trop Med Hyg*. 2009;103(4):423–4.
9. Ananthanarayan R, Paniker CJ. Ananthnarayan and Panikar's Textbook of Microbiology, 8th Edn. Hyderabad, India: Universities Press (India) Pvt. Ltd.; 2009.
10. Fort G, Benincovi C. Doxycycline and the teeth. *Lancet*. 1969;1(7598):782. doi:10.1016/s0140-6736(69)91787-5.
11. Andriopoulos P, Tsironi M, Deftereos S, Aessopos A, Assimakopoulos G. Acute brucellosis: presentation, diagnosis and treatment of 144 cases. *Int J Infect Dis*. 2007;11(1):52–7. doi:10.1016/j.ijid.2005.10.011.
12. Alshaalan MA. Brucellosis in children: Prevention, diagnosis and management guidelines for general pediatricians endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). *Int J Pediatr Adolesc Med*. 2014;1(1):40–6. doi:10.1016/j.ijpam.2014.09.004.

Author biography

Sneha S. Bowalekar, Consultant Microbiologist

Vijitha Vijaykumar, Post Graduate Student

Cite this article: Bowalekar SS, Vijaykumar V. Pyrexia of unknown origin: A microbiological review of cases in pediatric population at a tertiary care hospital. *IP Int J Med Microbiol Trop Dis* 2022;8(2):123-126.