

The article was received on July 9, 2021, and accepted for publishing on September 5, 2021.

VARIA

Clinical profile of Mediterranean fever – Study from an Indian tertiary care center

Varsha Somakumar¹, V.S. Srikanth², Cibi Manoharan¹, Vishal Marwaha¹, V.R. Mujeeb², M.G.K. Pillai¹, Anna M. Bastine¹, Mehana Ashraf¹

Abstract: *Introduction: Brucellosis is a zoonotic disease which is also known as Mediterranean fever. It is acquired from the handling of infected animals or consuming contaminated milk or milk products. The incubation period varies from 1-3 weeks to several months before clinical disease appearance and it shows multiorgan involvement. This study focuses on the varied presentation of this disease and laboratory findings. Materials and Methods: This is a retrospective study, where the past 15 years data of cases diagnosed with brucellosis was studied in a tertiary care center in South India. Patient demographics, clinical presentation, duration of stay in the hospital, hematological and biochemistry profiles were collected and analyzed in SPSS. Results: More number cases were found among the male gender (70%), mostly in the 20-40 years age group (40%). 95% of cases reported fever, 40% with arthralgia (29% generalized in nature), and 32% with a headache. A Positive Pearson correlation between CRP and NLR, and CRP and PLR were found, which was statistically significant. Mean laboratory values were documented. 37% of patients were found to have hepatosplenomegaly on ultrasound Conclusion: Most of the patients were admitted as cases with pyrexia of unknown origin. Our study focused on the different clinical presentations and laboratory findings of brucellosis and will help give a better understanding and outline during brucellosis case diagnosis and management in a cost-efficient manner.*

Keywords: *brucellosis, undulant fever, Mediterranean fever*

INTRODUCTION

Brucellosis is a zoonotic disease caused by bacteria of the genus *Brucella*. It is also known as undulant fever or Mediterranean fever [1]. Caused by Gram-negative coccobacilli, non-spore-forming and non-motile and aerobic; *B. melitensis*, *B. abortus*, *B. suis* are the important human pathogens. It is acquired from the handling of infected animals or consuming contaminated milk or milk products. Exposure is frequently occupational. Human brucellosis is either an acute febrile disease or a persistent disease with a wide variety of symptoms like night sweats, asthenia, insomnia, anorexia, and headache.

The disease is controlled by the routine practice of pasteurizing milk and milk products, as well as by comprehensive campaigns to eradicate the disease by destroying domestic animals which exhibit positive serologic reactions to brucellae. Vaccines providing some protection to cattle, sheep, and goats are available [2]. The incubation period of this infection is between 1-3 weeks but can take several months before clinical disease appearance [1]. The disease shows multiorgan involvement including musculoskeletal, digestive, urogenital, hematological, cardiovascular, respiratory, and central nervous systems [3]. According to the duration of symptoms, it can be classified

Corresponding author: V.S.Srikanth
dr.v.s.srikanth@gmail.com

¹ Amrita Institute of Medical Sciences, India

² Command Hospital Air Force, India

as acute (<8 weeks), sub-acute (8 to 52 weeks), and chronic (> 52 weeks).

Subacute brucellosis, typically presenting with undulant fever, described in endemic areas with localized infections such as epididymitis, orchitis, and osteoarticular complications, is most commonly seen. Osteoarticular involvement is the most common focal complication of brucellosis (10-85%) [4]. Sacroiliac joints are the most common site involved in younger patients; spondylitis and peripheral arthritis usually occur in older patients. Cardiovascular complications of brucellosis (endocarditis, myocarditis, and pericarditis) are rare (1% of cases) [5].

In humans, the most common route of entry of *Brucella* bacteria is through the gastrointestinal tract and it then localizes in the reticuloendothelial system. Hepatic enlargement is the most frequent gastrointestinal manifestation of brucellosis (32-63% of cases) [6]. Neurobrucellosis is the most serious complication of brucellosis with neither a typical clinical manifestation nor a specific cerebrospinal fluid (CSF) picture and mimics other neurological disorders leading to diagnostic dilemmas. The prevalence of Neurobrucellosis ranges from 1.7 to 10% of brucellosis worldwide [7].

This study aims to record the clinical features and cut off of certain laboratory values of human brucellosis cases in South India, for prompt diagnosis of the same.

MATERIALS AND METHODS

This is a retrospective observational study, where 15 years of data of patients diagnosed with brucellosis is collected in a pre-designed format. Details including demographics, clinical presentation, hematological and biochemistry profiles are collected and analyzed in SPSS. Inclusion criteria are patients diagnosed with brucellosis in our hospital, with positive IgM ELISA. Exclusion criteria include cases previously diagnosed from an outside hospital, patients who had taken the alternative form of treatment, etc to avoid bias in lab reports. Study design, data collection, and write-up were done in Amrita Medical College. Study analysis and review were done by V.S. Srikanth, using SPSS, where Pearson correlation and values of central tendency of the findings were recorded.

Data collection, analysis, and article preparation are done in accordance and with the permission of Amrita Institute's ethics review committee.

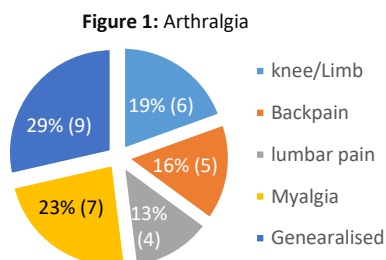
RESULTS

In our study, we found that 70% (54) were male and 30% (23) females, out of the total 77 cases. The age group of presentations were most in the 20-30 years group (22%); 30-40 years were 18% and remaining presentations were scattered across all other age groups (Table 1).

Table 1: Age distribution

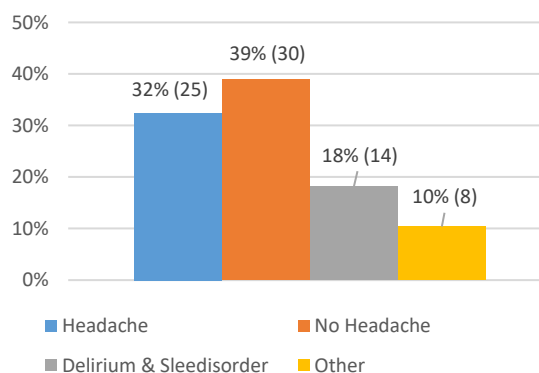
Age	< 17 years	20-30 years	30-40 years	40-50 years	50-60 years	> 60 years
Number	13	17	14	10	11	12
% distribution	17%	22%	18%	13%	14%	16%

5 cases were reported outside Kerala. The hospital stay duration was a minimum of 3 days and a maximum of 30 days, with a mean duration of 10 days. Clinical presentation – Fever - 73 (95%) patients presented with fever, out of which 50 (68%) had a high-grade fever (102-104). The fever duration was a minimum of 5 days to a maximum of 120 days and a mean duration of 21 days. Arthralgia – 31 (40%) patients presented with severe arthralgia, rest had no features of arthralgia (Figure 1).



The most common GIT presentation was Constipation and vague abdominal pain and headache were present in 32% (25) of patients (Figure 2).

Figure 2: CNS symptoms



Mean values of neutrophil, lymphocyte, platelet counts, red cell distribution width, mean platelet volume, C reactive protein (CRP), procalcitonin, hemoglobin, SGOT, SGPT,

serum protein, albumin, sodium, potassium, creatinine, and IgM Elisa values were found (Tables 2 and 3).

Table 2: Laboratory findings

Statistical Values	N (%)	L (%)	P (KU/ml)	RDW (%)	MPV (fL)	CRP (mg/L)	Procal (ng/mL)
Mean	56.32	31.79	303.01	14.95	8.39	61.58	0.78
Min Value	7.8	4.9	27.1	7	5	0.3	0.018
Max Value	90	72	687	27	25.8	306	5.3
Median	56	29.6	284.5	14.2	7.99	29.32	0.2
Std Deviation	17.33	16.12	147.01	3.09	2.99	72.46	1.42

Table 3: Laboratory findings – cont.

Statistical Values	Hb (g/dL)	SGOT (IU/L)	SGPT (IU/L)	Protein (g/dL)	Albumin (g/dL)	Na (mEq/l)	K (mEq/l)	Creat (mg/dL)	IgM ELISA (U/ml)
Mean	12.01	93.33	99.70	7.17	9.57	134.30	8.80	0.92	14.99
Min Value	6	9	9	5.33	1.77	120	2.7	0.05	0.8
Max Value	17.4	2142	2563	9.5	178.9	141.5	309	1.66	80.622
Median	12	36.35	51.5	7	3.7	134.55	4	1	5.5665
Std Deviation	2.31	253.51	293.64	0.84	27.77	4.12	37.82	0.32	20.65

Pearson correlation between CRP and neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) was found to be positive and statistically significant (Table 4, Figures 3 and 4 respectively). 37% (29) of patients were found to have hepatosplenomegaly on ultrasound.

Table 4: Pearson Correlation

		NLR	PLR
CRP	Pearson Correlation	0.476	0.579
	P value	0.001	0.001

Figure 3: Scatter Plot of Pearson Correlation between CRP and NLR

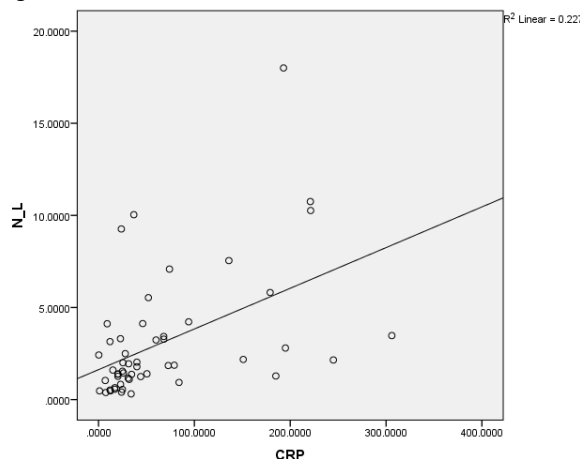
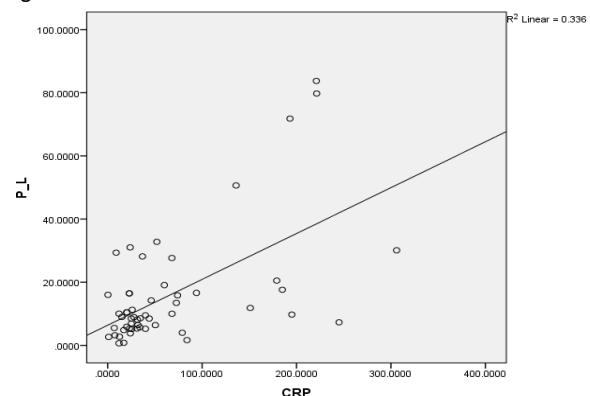


Figure 4: Scatter Plot of Pearson Correlation between CRP and PLR



DISCUSSION

A higher incidence of cases was seen among males in our study (54, 70.1%), comparable to similar studies [9, 10, 18].

The mean age of brucellosis patients in our study was 36.95±19.22 years, similar to the findings of Huseyin S et al. [19]. In another similar study done by Mahmood Nabavi et al. [7], the mean age was 39.59 ± 17.28 years, and the most prevalent age groups was 31–50 (42.1%), while in another study done by Akhvlediani T et al. [9], mean age was 39.9 (standard deviation = 15.1) years and 45% of participants were 21–40 years old, which is comparable to our result.

Common clinical presentations in our study were fever (73, 94.8%), arthralgia (31, 40.26%), and generalized pain and swelling with myalgia (33, 43%), consistent with other studies [18]. Abdominal pain, loss of appetite, loss of weight, vomiting, etc were seen in 34 (44.1%) cases, while other symptoms like headache, altered sensorium, and fatigue were seen in 28 (36.3%) cases. In a similar study done by Akhvlediani T et al. [9], the most frequent complaints were sweats (92%), joint pain (91%), aches (90%), malaise (90%), fatigue (87%), and rigors (86%), arthralgia (72%). Loss of appetite, weight loss, and arthritis was also observed in 46%, 44%, and 24% of participants, respectively. The most prevalent clinical manifestations of brucellosis were fever, anorexia, weight loss, low back, and muscle pains in the study by Mahmood Nabavi et al. [7] and another similar study done by Kazanasmaz H [11], arthralgia (45.8%), fever (≥ 38.5 C) (28.6%), and malaise and fatigue (11.5%) were the most common complaints at the time of presentation to the hospital [4].

29% of the patients with arthralgia presented with back pain, consistent with the findings of the study by Tasova Y et al. [15] and Turan H [16].

Mean neutrophil, lymphocyte, NLR, platelets, PLR, RDW, MPV, and CRP was found to be 56.3, 31.8, 3.22, 303, 15.67, 14.95, 8.39, and 61.58 respectively in our study. In a similar study done by Aktar F et al. [12], Neu – 71, Lym – 16, Plt – 282, NLR – 4.1, PLR – 154, RDW – 16.2, MPV – 8.2, and CRP – 28.1. NLR can be determined from routine blood differentials at no additional cost, it increases in inflammatory conditions and this increase is considered as an indicator of systemic inflammation [13]. Studies showed that platelets also play an active role in inflammation while having regulatory effects on the immune system [14].

A similar MPV of 8.6 and a mean platelet count of 246 were also seen in the study done by Okan DH et al. [14]. Thrombocytopenia and lower MPV values found in our study are consistent with findings of other similar studies [12, 14]. Considering the same, MPV values in combination with platelet counts might be useful in patients with brucellosis [14].

References

1. Hasanjani Roushan MR, Ebrahimpour S. Human brucellosis: An overview. *Caspian J Intern Med*. 2015 Winter;6(1):46-7. PMID: 26221498; PMCID: PMC4478120.
2. Alton GG, Forsyth JRL. Brucella. In: Baron S, editor. *Medical Microbiology*. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 28. PMID: 21413351

C-reactive protein assay is a helpful adjunct in the diagnosis of patients with brucellosis [17]. High levels of CRP (61.58), SGPT (93.3), SGOT (99.7) was seen in our study, similar to the high CRP (39%), high ALT (33%), and high AST (20%) found in the study done by Shi et al. [18]. A positive correlation between standard agglutination titer and SGOT and SGPT was found by Huseyin S et al. [19].

AST, ALT, and CRP levels were found to be elevated in 27.6%, 21.6%, and 69.6% of the patients, respectively, and leukopenia (21.4%), thrombocytopenia (23%), and anemia (70%) in the study by Guler et al. [20]. 37% of patients were found to have hepatosplenomegaly on ultrasound, consistent with findings from a similar study done by Shi et al. [18].

Limitations

Only 77 cases could be included in the study. Not all the patients had all the laboratory tests done. Correlations were only weakly positive.

CONCLUSION

The most common clinical presentation of brucellosis was fever, arthralgia, abdominal pain, and headache. Elevated levels of CRP, procalcitonin, NLR, SGOT, and SGPT with thrombocytopenia and decreased levels of MPV were seen. A positive and significant correlation of CRP with NLR and PLR was also seen. Our study focused on the different clinical presentations and laboratory findings of brucellosis and will help give a better understanding and outline during brucellosis case diagnosis and management, in a more prompt manner.

Contribution of authors

Varsha Somakumar, V S Srikanth, Cibi Manoharan – concepts, design, the definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, editing, and review; Vishal Marwaha, VR Mujeeb, M.G.K.Pillai – concepts, design, the definition of intellectual content, Manuscript editing and review; Anna Maria, Mehana Ashraf – data acquisition, data analysis, manuscript preparation, editing.

The manuscript has been read and approved by all the authors and each author believes the manuscript represents honest work. There is no conflict of interest among the authors.

3. Corbel, M. J, Food and Agriculture Organization of the United Nations, World Health Organization & World Organisation for Animal Health. (2006). *Brucellosis in humans and animals*. World Health Organization. <https://apps.who.int/iris/handle/10665/43597>
4. Mehmet Doganay and Bilgehan Aygen, Human brucellosis: an

- overview., *Int J Infect Dis* 2003; 7: 173-182, [https://www.ijdonline.com/article/S1201-9712\(03\)90049-X/pdf](https://www.ijdonline.com/article/S1201-9712(03)90049-X/pdf)
5. Young EJ. *Brucella* species. In: *Principles and Practice of Infectious Diseases*. 7th edition. Edited by Mandell GL, Bennett JE, Dolin R. Philadelphia: Churchill Livingstone; 2010: 2: 2921-25
 6. Aziz S, Al-Anazi AR, Al-Aska AI. A review of gastrointestinal manifestations of Brucellosis. *Saudi J Gastroenterol* 2005; 11: 20-7, DOI: 10.4103/1319-3767.33333
 7. Nabavi M, Hatami H, Jamaliarand H. Epidemiological, risk factors, clinical, and laboratory features of brucellosis in the Southwest of Iran within 2009–2015. *Int J Prev Med* 2019;10:108, DOI: 10.4103/ijpvm.IJPVM_14_18
 8. Maji S, Manjunath N, Bahubali VH, et al. Neurobrucellosis: A neglected entity? An update from tertiary care Neurocentre of South East Asia. *J Neurol Sci.* 2020;411:116683. doi:10.1016/j.jns.2020.116683
 9. Akhvlediani T, Bautista CT, Garuchava N, Sanodze L, Kokaia N, Malania L, et al. (2017) Epidemiological and Clinical Features of Brucellosis in the Country of Georgia. *PLoS ONE* 12(1): e0170376. <https://doi.org/10.1371/journal.pone.0170376>
 10. Havas KA, Ramishvili M, Navdarashvili A, Imnadze P, Salman M. The human-animal interface of domestic livestock management and production and its relationship to brucellosis in the country of Georgia 2010: a rapid assessment analysis. *Prev Vet Med.* 2012; 105(1–2):10–6. pmid:22405190
 11. Kazanasmaz H, Geter S. Investigation of the Sensitivity and Specificity of Laboratory Tests Used in Differential Diagnosis of Childhood Brucellosis. *Cureus.* 2020 Jan 23;12(1):e6756. doi: 10.7759/cureus.6756. PMID: 32140324; PMCID: PMC7039374.
 12. Aktar F, Tekin R, Bektaş MS, Güneş A, Köşker M, Ertuğrul S, Yılmaz K, Karaman K, Balık H, Yolbaş İ. Diagnostic role of inflammatory markers in pediatric *Brucella* arthritis. *Ital J Pediatr.* 2016 Jan 11;42:3. doi: 10.1186/s13052-016-0211-5. PMID: 26753565; PMCID: PMC4709903.
 13. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med.* 2012;5(1):2. Published 2012 Jan 26. doi:10.1186/1755-7682-5-2
 14. Okan DH, Gökmen Z, Seyit B, Yuksel K, Cevdet Z, Deniz A. Mean platelet volume in brucellosis: correlation between brucella standard serum agglutination test results, platelet count, and C-reactive protein. *Afr Health Sci.* 2014;14(4):797–801. doi:10.4314/ahs.v14i4.4
 15. Tasova Y, Saltoğlu N, Sahin G, Aksu HSZ. Osteoarthricular Involvement of Brucellosis in Turkey. *Clin Rheumatol.* 1999;18:214–219. DOI:10.1007/s100670050087
 16. Turan H, Serefhanoglu K, Karadeli E, Togan T, Arslan H. Osteoarticular involvement among 202 brucellosis cases identified in Central Anatolia region of Turkey. *Intern Med.* 2011; 50(5):421-8. Epub 2011 Mar 1. PMID:21372451
 17. Navarro JM, Mendoza J, Leiva J, Rodriguez-Contreras R, de la Rosa M. C-reactive protein as a prognostic indicator in acute brucellosis. *Diagn Microbiol Infect Dis.* 1990;13:269–270 PMID: 2023294
 18. Shi, Y., Gao, H., Pappas, G., Chen, Q., Li, M., Xu, J., Lai, S., Liao, Q., Yang, W., Yi, Z., Rouzi, Z., & Yu, H. (2018). Clinical features of 2041 human brucellosis cases in China. *PLoS one*, 13(11), e0205500. <https://doi.org/10.1371/journal.pone.0205500>
 19. Huseyin Sahinturk, Bulent Baran, Gurhan Sisman and Reskan Altun, Liver involvement is associated with blood culture positivity and high agglutination titre in patients with brucellosis in Turkey, , *Journal of Medical Microbiology* 2018;67:1078–1082 DOI 10.1099/jmm.0.000791
 20. Guler S, Kokoglu OF, Ucmak H, Gul M, Ozden S, Ozkan F (2014) Human brucellosis in Turkey: different clinical presentations. *J Infect Dev Ctries* 8:581-588. doi: 10.3855/jdc.3510.