Original Research Paper Clinical Research

Children with prolonged fever attending tertiary level health facility in South India :A clinicoepidemiological analysis.

Sheeja Sugunan	DCH, DNB (Paediatrics), FPIC (post doctoral fellowship in paediatric Intensive care), Assistant Professor, Department of Paediatrics, Government Medical College, Thiruvananthapuram.
Nibin Nahaz	MD (Paediatrics), Department of Paediatrics, Government Medical College, Thiruvananthapuram.
Rajamohanan K Pillai	MD (Paediatrics), Professor of Paediatrics, Department of Paediatrics, Government Medical College, Thiruvananthapuram.
Santhosh Kumar A	MD Professor of Paediatrics Government, Medical College, Thiruvananthapuram.

ABSTRACT

Objectives: To study the changing epidemiology in terms of aetiology and clinical profile of prolonged fever of more than 7 days duration in a tertiary care hospital during a period of 10 years. Method: All children admitted with undiagnosed fever of more than 7 days during the period January 2000 to December 2000 and January 2012 to October 2013.were included in the study and data collected prospectively. **Results:** 80 children were admitted during the period January 2000 to February 2001and231 patients were admitted during the period January 2012 to October 2013 with prolonged fever. Male to female ratio was 55:45 in 2000 and 51.5: 48.5 in 2012. There were significantly ($p<0.01$) more children with fever duration more than 4 weeks in 2000 (33.5%) compared to 2012 (6.5%). In both groups infection was the commonest cause of prolonged fever. Dengue fever was noted to be commonest cause of prolonged fever in 2012 (33%), while enteric fever was the commonest in 2000. There were no cases of dengue or scrub typhus in 2000. Malignancy accounted for 5% of cases in both the groups. There was a significant decrease in the number of undiagnosed cases($p<0.01$) from 20% in 2000 to 10 % in 2012 and fever lasting for more than 3 weeks also decreased from 33% to 7%. **Conclusion:** Infection continues to be the commonest cause of prolonged fever in children but the etiology of infection changes significantly in a span of 10 years. Proportion of undiagnosed cases and fever lasting for more than 3 weeks has come down significantly over the years probably due to changing trends in diseases pattern and access to newer diagnostic modalities.

KEYWORDS :

Introduction

Fever of more than 1 week duration without an apparent diagnosis is a diagnostic challenge for any physician. The delay in reaching a diagnosis leads to delay in initiation of proper treatment which may also adversely affect the patient outcome. The clinical and etiological profile of prolonged fever was studied in detail in many studies [1-12] since its first description by Petersdorf and Beeson in 1961[13]. Geographical and seasonal variations often determined the difference in disease profile [14] The aetiology of prolonged fever also varies from time to time as new diseases emerge and old ones are tackled with vaccination and other preventive measures. Changing trends of prolonged fever and the causes prevailing in a specific locality has not been found to be studied. This study was undertaken to describe the changing epidemiology in terms of aetiology and clinical profile of prolonged fever of more than 7 days duration in a tertiary care hospital during a period of 10 years. The knowledge of changing aetiology, outcome and varying clinical presentations of prolonged fever in a particular region helps the physician in finding a systematic and timely approach to the diagnosis and treatment of prolonged fever.

Methods

The study was carried out in the department of Paediatrics SAT Hospital, Government Medical College Thiruvananthapuram during the period of January 2000 to December 2000 and January 2012 to October 2013. After getting clearance from institutional ethical committee, all children admitted with undiagnosed fever of more than 7 days and at least one documented fever of greater than 38.3^0 C within 48 hrs of admission were enrolled in the study. Diagnosed cases of immunodeficiency, absolute neutropenia, fever cases with already determined aetiological diagnosis and fever with definite localising signs were excluded from the study.

All patients were subjected to a detailed clinical history and repeated physical examination. Basic investigations included haemoglobin, total and differential leucocyte count, peripheral smear , routine urine examination, blood culture, mantoux and chest x-ray. Specific investigations were conducted as guided by clinical clues. Data was collected in a prospective manner from all consecutive cases that met inclusion and exclusion criteria using pre designed proforma.

Results

Out of the total admission of 8397 patients, 80 children were admitted during the period January 2000 to February 2001 and out of the total admission of 16,497 patients, 231 patients were admitted during the period January 2012 to October 2013 with fever of more than 1 week duration with no apparent diagnosis. Both groups showed a slight male preponderance in the total number of cases. Male to female ratio was 55:45 in 2000 and 52: 49 in 2012 (table 1).

In both the groups majority of fevers subsided within 3 weeks. There were significantly ($p<0.01$) more children with fever duration more than 3 weeks in 2000 (33%) compared to 2012 (7%). In both groups infection was the commonest cause of prolonged fever. 20% of cases of prolonged fever were undiagnosed in 2000 while 10% of cases in 2012 did not have a definitive diagnosis ($p<0.01$).

Among the infectious causes typhoid fever (15%) was the commonest cause in 2000 while dengue fever (33%) was the commonest cause in 2012. There were no cases of dengue fever and scrub typhus infection in 2000, while in 2012 there were 18 cases (8%) of scrub typhus and 76 cases (33%) of dengue fever. Among children with enteric fever hepatomegaly was commoner than splenomegaly in both groups. There was no case of confirmed malaria in 2000 while 4 children had responded to empirical chloroquine therapy in 2000 while in 2012 there were 12 cases (5.2%) of confirmed malaria. In both groups Leptospirosis was the cause of prolonged fever in less than 5% cases.

Leukaemia was the only malignancy which presented as prolonged fever .High absolute neutrophil count was significantly more common in children with bacterial infection ($P<0.01$). Significant

leucocytosis with total count more than 15000cells / mm3 was present in 44% of acute leukaemia and all cases of SOJIA and Kawasaki disease. .All cases of malignancy in both the groups had anaemia. ESR above 85mm in 1st hour was observed in all cases of leukemia, systemic onset juvenile idiopathic arthritis, Kawasaki disease and systemic lupus erythematosis in both the groups. Markedly elevated ESR (>100mm in 1st hour) was seen in 23 cases (50%) of malignancy and collagen vascular disease and 7 (2.4%) cases with other diseases. Markedly elevated ESR > 100mm in 1st hour, thus had a sensitivity of 50% and specificity of 97% with 79% positive predictive value and 91.8% negative predictive value for malignancy and collagen vascular diseases. Mantoux in tuberculosis showed 80% sensitivity, 94.6% specificity, 50% positive predictive value and 98% negative predictive value. IMN which accounted for 2.5% cases in 2000 increased to 11% (P<0.05) in 2012.

Discussion

Fever of more than 7 days is an important diagnostic challenge to any physician. In the present study there was no significant difference in sex ratio in children presenting with prolonged fever of more than 1 week. The age distribution was skewed with more proportion of older age groups. Children less than 3 years constituted less than 15% of cases in both the periods studied, this may be due to early reference of younger children and lesser incidence of malignancy and collagen vascular disease in younger children. In the study by Guillermo Chantana et al [15] the mean age reported was 64 months.

The general pattern of prolonged diagnosed fever was similar to other published studies from developing countries [14,16]. Infection continued to be the commonest cause of undiagnosed fever in both the periods studied, as has been described in many other studies, but the aetiology of infection has shown a significant change over the years. The incidence of malignancy and collagen vascular disease as causes of prolonged fever has remained same over the 10 year period in our study. Mouaket et al [17] and Brewis et al [18] also reported a similar proportion of cases with malignancy. There was a significant decrease in the number of undiagnosed cases, from 20% in 2000 to 9.5% in 2012 (P<0.01) probably due to availability of more sensitive newer diagnostic tools.

Among the infectious causes Dengue fever was noted to be commonest cause of prolonged fever in 2012 accounting for 33% of cases of undiagnosed prolonged fever. The high incidence of dengue fever in our study coincided with the Dengue epidemic that hit south India during 2012 – 2013. There were no cases of Dengue fever in 2000. Enteric fever as a cause of pronged fever decreased from 15% to 9 % probably due to early diagnosis due to availability of better culture methods or decrease in incidence due to immunisation and better hygienic practices. There were no cases of scrub typhus in 2000 while it was responsible for 8% of cases of prolonged fever in 2012. Tuberculosis as a cause of prolonged undiagnosed fever showed a decreasing trend from 6% in 2000 to 1.7% in 2012 probably due to sensitive early diagnostic tools for Tuberculosis.

In the study by Amy chow et al [14]the major individual cause was Brucella followed by Typhoid and Tuberculosis, while in the study by D Bandyopadhyay [19] et al tuberculosis was the commonest cause. Thus even though infection is the commonest cause in most studies the disease profile is different in different studies from different geographical areas. Our study brings to light the fact that disease profile can change even within a short time period of 10 years in a particular place as newer diseases are imported and older ones tackled with effective treatment and preventive strategies. While Tuberculosis and Enteric fever as causes of prolonged undiagnosed fever decreased in incidence there has been an increase in IMN, Dengue fever and scrub typhus.

Leukaemia was the only malignancy which presented as prolonged fever in both the years studied. In the study by R H Hassan et al [20] also leukaemia was the commonest malignancy which presented as prolonged fever but it was not the only malignancy. All cases of leukaemia had anaemia and elevated ESR of more than 85mm in 1st hour in our study. Markedly elevated ESR (>100mm in 1st hour) in malignancy and collagen vascular disease had 79% positive predictive value and 91.8% negative predictive value.

95% of patients had potentially diagnostic clues (PDC), but they were found to be misleading in 31%. De Kleijn et al[21] in their study of 107 patients with FUO found potentially diagnostic clues in 97% cases with in 1 week of admission but 30% were misleading.PDC 's encountered most commonly include myalgia, abdominal complaints, generalised and cervical lymphadenopathy, hepatomegaly and splenomegaly.

There was a significant decrease in incidence of fever lasting for more than 3weeks in 2012 compared to 2000 probably due to changing disease pattern, access to advanced diagnostic tools and early appropriate treatment. This is also reflected in the decrease in number of undiagnosed cases (P<0.05) in 2012 compared to 2000. The overall outcome was good in agreement with other studies, there was only 1 mortality in 2000 the etiological cause couldn't be established in this case.

CONCLUSIONS

Infectious diseases continue to be the commonest cause of prolonged fever in children. Disease profile can change significantly in the same place even in a small span of 10 years. Atypical presentation of emerging diseases should be considered as a common cause of prolonged fever. There was a significant decrease in number of undiagnosed cases and cases of fever lasting for more than 3 weeks probably due to changing disease pattern, access to advanced diagnostic tools and early appropriate treatment.

Table 1 : Comparative clinical presentation of prolonged fever in 2000 and 2012

	2000 Number (%)	2012 Number (%)
1to 3yrs	10 (12.5%)	32 (14%)
4to 6yrs	36 (45%)	66 (29%)
7 to 12yrs	34 (42.5%)	133 (58%)
Fever more than 3 weeks	26 (33%)	15 (7%)
Infection	53 (67%)	174 (75%)
Collagen vascular diseases	6 (7%)	23 (10%)
Malignancy	4 (5%)	12 (5%)
Undiagnosed	16 (20%)	22 (10%)
Dengue	0 (0%)	76 (33%)
Enteric fever	12 (15%)	20 (9%)
Tuberculosis	5 (6%)	4 (1.7%)
Leptospirosis	4 (5%)	7 (3%)
Scrub typhus	0 (0%)	18 (8%)
IMN	2 (2.5%)	24 (11%)
Hepatomegaly	23 (29%)	92 (40%)
Splenomegaly	14 (18%)	50 (22%)
Lymphocytosis	48 (60%)	194 (84%)
Anaemia	46 (58%)	115 (50%)
Total cases	80	231

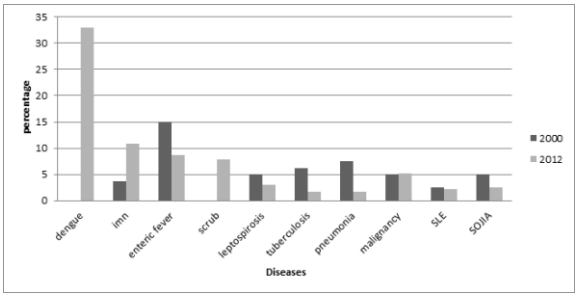

Fig 1: Proportion of each disease in 2000 and 2012

References

1. Larson EB, Featherstone HJ, Petersdorf RG, Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. Medicine 1982; 61: 269–92.
2. Knockaert DC,Vanneste LJ,Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum.Arch Intern Med 1992; 152: 51–55
3. Iikuni Y, Okada J, Kondo H, Kashiwazaki S. Current fever of unknown origin 1982–1992. Intern Med 1994; 33; 67–73.
4. de Kleijn EMHA, van der Meer JWM. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995; 47; 54–60.
5. De lewis, Fransisco Steen,MD Fever unknown. BMJ 1996;39:257-60.
6. Druack DT, Streat AC. Fever of unknown origin reexamined and redefined. Curr Clin Top Infect Dis. 1991;11:35-51.
7. Paul M Arnow, John P Flaherty . Fever of unknown origin . lancet.1997;350(e.g. 2):575-580
8. Feigin RD, Shearer WT. Fever of unknown origin in children. Curr Probl Pediatr 1976;6(10): 1-65.
9. Gratz S, Behr TM, Herrmann A, Meller J, Conrad M, ZappelH, et al. Immunoscintigraphy (BW 250/183) in neonates and infants with fever of unknown origin. Nucl Med Commun 1998;19:1037-1045.
10. Rico Mari E, Andreu Alapont E, Guillamon T, Calvo Penadesl, Sanchez Lorente A. Fever of unknown origin in children: results of a diagnostic protocol. An Esp Pediatr 1994;41:155-158.
11. Steele RW, Jones SM, Lowe BA, Glasier CM. Usefulness of scanning procedures for diagnosis of fever of unknown origin in children. J Pediatr 1991;119:526-530.
12. Cruz Guerrero G, Navarro González J, Cintado Bueno C. Fever of unknown origin in children. An Esp Pediatr 1978;11:683-692.
13. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30.
14. Amy Chow, Joan L Robinson, Fever of unknown origin in children: a systematic review. World J Pediatr 2011;7(1):5-10
15. Guillermo chantada, Sandra casak, jose daza plata, juan pociecha, rosa bologna. Children with fever of unknown origin in argentina : an analysis 0f 113 cases. pediatr infect dis j.1994;13(4):260-263
16. Joshi N, Rajeshwari K, Dubey AP, Singh T, Kaur R. Clinical spectrum of fever of unknown origin among Indian children.Ann Trop Paediatr 2008;28:261-266.
17. Mouaket AE, el-Ghanim MM, Abd-el-Al YK, al-Quod N.Prolonged unexplained pyrexia: a review of 221 paediatric cases from Kuwait. Infection 1990;18:226-229.
18. Brewis EC. Undiagnosed fever. BMJ 1965;1:107-9.
19. D Bandyopadhyay, Ramtanu Bandyopadhyay, Rudrajit Paul, and Deeptarka Roy, Etiological Study of Fever of Unknown Origin in Patients Admitted to Medicine Ward of a Teaching Hospital of Eastern India.IMJ 2007;22:342-8.
20. Hassan RH, Fouda AE, Kandil SM. Fever of unknown origin in children: a 6 year-experience in a tertiary pediatric Egyptian hospital. Int J Health Sci Qassim. 2014;8(1):13-9.
21. de Kleijn EMHA, van der Meer JWM. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995; 47; 54–60.