Etiology of Fever of Unknown Origin in Children from Mumbai, India

This descriptive study evaluated 49 children with fever lasting for more than 7 days at a tertiary hospital in urban Mumbai. Etiologic diagnosis could be established in 88% of the cases. Infections were the causein 34 (79%)patients, 6 (14%) were diagnosed as collagen vascular diseases, and 3 (7%) had other cause.

Keywords: *Enteric fever, Pyrexia of unknown origin, Tuberculosis.*

There is paucity of recent data on the etiology of fever of unknown origin (FUO) in Indian children. This descriptive study prospectively enrolledconsecutive children aged 3 months to 18 years with FUO presenting to the outpatient department of a tertiary care private hospital in Mumbai November 2014 and April 2015. FUO was defined as fever ≥38.3ºC lasting for more than 7 days where history, examination and preliminary investigations, including complete blood count (CBC), malarial parasite (MP), urine routine examination, Chest *X*-Ray, ultrasound abdomen were normal [1]. Children with nosocomial FUO, primary immuno-deficiency disorders and human immuno-deficiency virus infection were excluded. Further investigations were performed in accordance with the usual clinical care pathway. The diagnosis was considered confirmed if it met the gold standard for the illness (culture, molecular diagnosis, specific IgM serology or standard diagnostic criteria for non infectious diseases). The diagnosis was considered probable if clinical, radiologic or laboratory criteria were satisfied but the gold standard was negative or was unavailable. The study was cleared by the hospital Research and Ethics Committee which granted waiver of informed consent from the study participants.

Forty-nine children (23 males) were included in the study with a mean age of 8 years (range 11 mo - 17 y). The median (range) duration of fever prior to presentation 14 (8-60)day. A diagnosis could be established in 43 patients; in 27 the diagnosis was 'confirmed' and in 16 it was 'probable'. Infections were diagnosedin 34 (79%) patients, while 6 (14%) had collagen vascular diseases and 3 had other causes.

The commonest infection was tuberculosis (TB) accounting for 12 cases (Pulmonary TB 6; lymph node TB 4; one each of disseminated and bone TB) Contrast enhanced computed tomography (CECT) emerged as an important diagnostic investigation, picking up findings suggestive of TB in 6 patients who had normal *X* -rays and ultrasoundscans. The diagnosis was bacteriologically confirmed in six out of 12 TB cases (cultures in 5 and Xpert MTB/Rif in 6). Three cases were rifampicin susceptible while two isolates were multi-drug resistant, and one isolate was extensively drug-resistant. The other infectious causes were viral infections in 8 (18%) (Epstein Barr Virus infection in 2, probable viral infections 6), enteric fever in 7 (16%), bacterial sinusitis in 4 (9%), and rickettsial fever, *S. aureus* osteomyelitis and atypical pneumonia in oneeach. The collagen vascular disease included systemic onset juvenile rheumatoid arthritis in 2, Kawasaki disease in 2, and reactive arthritis and dermatomyositis in one each. The miscellaneous group included erythema nodosum in one and drug-related hypersensitivity syndrome in two patients. In six cases where the diagnosis could not be established, fever resolved in 3 cases, continued in 2, and 1 patient was lost to follow up. At the end of the study 43 patients were free of fever; there was no mortality.

Tuberculosis emerged as the commonest cause of FUO in our study; in patients presenting with fever lasting for more than 2 weeks half the etiology was TB. This is in agreement with adult studies on FUO from India [2,3]. An interesting finding of our study was bacterial sinusitis as an etiology of FUO in the absence of prominent upper respiratory signs; diagnosis was established by a CT of paranasal sinus in children with FUO and high leukocyte count with no other septic focus.

The study results may not be generalizable as regional infections influence etiology [4]. Asthe study was conducted at a tertiary care center, infections such as malaria, urinary tract infections did not figure in the etiology as they were diagnosed and treated prior to referral. The high prevalence of drug resistance in TB is again possibly due to referral bias. The absence of malignancy as cause of FUO is probably due to the small study size.

The study suggestsCECT as an important diagnostic investigation in patients with FUO. The high prevalence of drug-resistant TB in the study emphasizes the need for establishing a bacteriologic diagnosis of TB and avoiding empirical therapy.

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REFERENCES

1. Palazzi DL. Fever without source and fever of unknown origin. *In* Cherry JD, Harrison GJ, Kaplan AL, Steinbach WJ, Hotez PJ, editors. Textbook of Pediatric Infectious Diseases, 7th ed. Philadelphia: Elsevier Saunders; 2014.p.837-8.
2. Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. J Postgrad Med. 2001;47:104.-7.
3. Bandyopadhyay D, Bandyopadhyay R, Paul R, Roy D. Etiological study of fever of unknown origin in patients admitted to medicine ward of a teaching hospital of eastern India. J Glob Infect Dis. 2011;3:329-33.
4. Joshi N, Rajeshwari K, Dubey AP, Singh T, Kaur R. Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Paediatr. 2008;28:261-6.

Hypoferremic State in Overweight and Obese Children

Children with high body mass index (BMI) are at risk of iron deficiency. In present study, 71 children with overweight or obesity were screened for iron deficiency. Mean BMI, ferritin and plasma soluble transferrin receptor (sTrfR) levels were 26.1 kg/m^2, 41.9 µg/L and 0.375 mg/L, respectively. Twenty (28%) children had anemia, and 44 (62%) had an underlying hypoferraemic state.

Keywords: *Anemia, Body Mass Index, Iron deficiency.*

Obesity is a low grade chronic inflammatory state with subclinical elevated levels of cytokines like IL-1b and TNF-á, which can affect iron sequestration and lead to a state of functional iron deficiency [1]. In addition children who are overweight or obese are at high risk of development of true iron deficiency primarily due to deficient iron intake and food fads and also due to deficient stores because of increased iron requirement owing to their larger blood volume [2]. The present study was undertaken to screen overweight and obese children in our institute for true hypoferraemic state based on serum ferritin and soluble transferrin receptor levels.

This cross-sectional study was conducted on 71 children aged 2-14 years between July 2015 to June 2016. Body mass index (BMI) was determined by calculating body weight/height^2 (kg/m^2), and BMI Z scores (BMIZ) were estimated using WHO reference charts. Enrolled cases were divided into overweight (BMIZ +1 to +2), obese (BMIZ +2 to + 3) and morbid obesity (BMIZ +3 Z). Anemia in 2-14 year age group and the ferritin cut-off to define hypoferraemic state were based on WHO criteria [3]. Plasma soluble transferrin receptor assay (sTrfR) was performed using sandwich ELISA method (Sincere Biotech). We had established a normal range for pediatric sTrfR assay in our healthy cohort as 0.17-2.1 mg/L [4]. Iron deficiency (ID) was defined as combination of either normal hemoglobin (Hb) for age and ferritin <30 µg/dL or normal for age and sTrfR levels >2.1 mg/L, while iron deficiency anemia (IDA) was defined as low Hb for age and ferritin <30 µg/dL or low Hb for age and sTrfR levels >2.1 mg/L. This study was approved by the ethics committee of the institute.

The demographic and hematological parameter are detailed in ***Table* I.** Serum ferritin was low in 44 (62%), normal in 25 (35%), and high in only 2 (3%) children.Among these, 69 (97.2%) had normal transferrin receptor level and only one child each had high or low levels. Anemia was noted in 20 (28%) cases; however, a hypoferraemic state could be identified in 44 (62%) cases. Out of 20 cases with anemia, 7 (35%) had anemia of chronic disease while 13 (65%) had iron deficiency anemia. In 44 cases with hypoferraemic state, 31 (70%) had evidence of iron deficiency alone and 13 (30%) had iron deficiency anemia. Anemia and hypoferraemic state was noted to be present in all three groups without any statistical difference (***Table* I**). The mean sTrfR level among three groups had a rising trend but the difference was not statistically significant.

As studies from our subcontinent have been limited on normal reference ranges for sTrfR levels in pediatric age groups as well as its utility in diagnosing iron deficiency in inflammatory states, a higher ferritin cut-off (<30ug/L), as suggested by WHO [3], was used in this study to define hypoferremic state. Gartner, *et al*. [5], have recently highlighted the importance of using a correction factor for