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Etiologic Agents of Pyrexia of Undetermined Origin Among Patients Attending a University Health Care Facility in Ogun State, Nigeria

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Abstract: This study investigated the etiologic agents of pyrexia of undetermined origin among patients attending University Health Care facility in Ogun State, Nigeria using standard techniques. Results obtained revealed that the age groups 26-30 and 21-25 were the most affected by pyrexia of undetermined origin for both male and female respectively while the least affected groups however for both male and female were the age groups 31-35, 46-50 and 51-55. 52 subjects had bacterial infection only, 23 had both bacteremia and malaria while 211 showed positive test to malaria parasitemia only. 14 subjects were found harboring neither bacterial infection nor malaria. *Salmonella typhi* was the most predominant of the isolated organisms with a prevalent rate of 24(32%), followed by *Pseudomonas aeruginosa* 18 (24%) and then both *Klebsiella pneumoniae and Staphylococcus aureus,* both with prevalent rate of 9(12%). In all the subjects, a total of 75 bacteria belonging to six different genera were recorded. It can therefore be concluded based on the results of this study that bacteremia is second only to malaria as the cause of pyrexia of undetermined origin in the studied area.

Key words: Etiology · Pyrexia · Bacteria · Malaria

INTRODUCTION

Adult patients frequently present to the physician's office with fever of temperature higher than 38.3°C [100.9°F]) [1]. This condition is readily diagnosed on the basis of presenting symptoms and a problem-focused physical examination. Occasionally, simple testing such as a complete blood count or urine culture is required to make a definitive diagnosis [2]. The definition of this type of fever as based on a case series of 100 patients, calls for a temperature higher than 38.3°C on several occasions to be regarded to as pyrexia and because the etiologic agents are not known on several cases while it lasted for more than three weeks prior to making a definitive diagnosis lead to the reason why it is popularly called pyrexia of undetermined origin. Some experts have argued for a more comprehensive definition of pyrexia of unknown origin that takes into account medical advances and changes in disease states, such as the emergence of human immunodeficiency virus (HIV) infection and an increasing number of patients with neutropenia. Others contend that altering the definition would not benefit the evaluation and care of patients with PUO [3].

According to Axelrod and Diringer [4], this infection is also known as fever or controlled hyperthermia and is commonly characterized by an elevation of temperature above normal range 36.5°-37.5°C due to an increase in body temperature regulatory set point [5]. This increase in set point triggers increase in muscle tone and shivering.

PUO remains the leading cause of morbidity and mortality among the populace, especially in sub-Saharan Africa [6]. The World Health Organization (WHO) defines PUO as an acute illness characterized by a rise in body temperature. The spectrum of diseases causing PUO not

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only seems to be determined by geography factors, but also to change with time [7]. The condition is a diagnostic challenge and as such constitutes a significant number of referrals to tertiary care centers. Previous studies have described the spectrum of the disease to be mainly secondary to infectious, neoplastic and inflammatory diseases [8]. The diagnostic work up for PUO is well described [9]. But there is no 'gold standard' and it may be done differently depending on the clinical situation. In most cases, it begins by confirming the presence of fever in hospital. A minimal work up includes a complete history including drug history, physical examination and investigations including complete blood count with differential blood film, routine blood chemistry, urinalysis and microscopy, blood and urine cultures, anti nuclear antibodies. rheumatoid factor, HIV antibodies, chest X-ray and hepatitis serology.

It is a prominent symptom of many diseases in human and animals with different microbial etiologies including bacteria, viruses and protozoa. It is considered a medical emergency as it may indicate a serious underlying condition or lead to significant side effects [10]. This present study was aimed at determining the common etiological agents of pyrexia of undetermined origin among patients attending a University medical care facility in Ogun State, Nigeria.

MATERIALS AND METHODS

Inclusion Criteria: Total number of 300 [138 male and 162 female] patients attending a University Health Care facility in Ogun state between the year 2010 to 2013 and with symptoms and signs suggestive of pyrexia or history of recent fever were recruited into this study following due consent of the subjects and ethical approval from the University health care facility ethical Committee.

Exclusion Criteria: Subjects already placed on antibiotics and/or antimalarial drugs were excluded from this study

Collection of Blood Samples: 7ml venous blood collection from each subject was carried out on scheduled days using a tubing tourniquet tied to the upper arm of each of the patient prior to cleaning before blood samples was collected.

Bacteriological Examination: Collected blood samples (5ml) were dispensed into Thioglycollate broth medium. Growth from broth cultures were sub-cultured onto surfaces of selective and differential agar media of Blood Agar, Chocolate agar, MacConkey's Agar, Salmonella - Shigella Agar and Mannitol Salt Agar. Chocolate Agar plate was incubated in the presence of 10% CO_2 using candle jar at 37°C for 24 hours while other Agar plates were incubated aerobically at 37°C for 24 hours. The following day, plates were examined for growth and characteristics colonies of different aerobic organisms grown on them. The identification of the isolated organisms was done following standard microbiological technique [11].

Parasitological Assay

Preparation of Blood Films: The laboratory method employed for staining and identification of malaria parasites in collected blood samples was done as described by [11]. Both thick and thin films were prepared. The thick film was prepared first because concentration of parasites is ensured by this type of blood film.

Examination of Blood Films: Both thick and thin smears prepared were examined microscopically under oil immersion. The immersion oil was spread to cover about 10mm in diameter in the areas of the film. With the (X100) objective the stained slides were examined for malaria parasites.

RESULTS

Table 1 depicts the frequency distribution of the studied age groups and their genders. As shown in the table, the studied age groups were delineated into eight categories as follows; 16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50 and 51-55. Of these age groups, age groups 26-30 and 21-25 were the most affected for PUO for male and female respectively. The least affected groups for both male and female were the age groups 31-35, 46-50 and 51-55. Overall, 138 male and 162 female were recruited for the study to make a total of 300 subjects. Of these 300 subjects, 52 had bacterial infection only, 23 had both bacterial and malarial infection, 211 shows positive test to malaria parasitaemia while only 14 subjects had neither bacterial nor malarial infection (Table 2). The prevalence of bacteria among the studied subjects revealed *Salmonella typhi* as the most predominant with a prevalent rate of 24 (32%), followed by *Pseudomonas aeruginosa* 18 *(*24*%)* and then both *Klebsiella pneumoniae and Staphylococcus aureus* with prevalent rate of 9(12%). In all the subjects, a total of 75 bacteria belonging to six different genera were recorded (Table 3).

Table 1: Frequency distribution of age group and gender of patients with Pyrexia of Unknown Origin

Age	Gender					
	Male		Female		Total	
Years	n	(%)	n	(%)	N	(%)
16-20	15	(10.87)	30	(18.51)	45	(15)
21-25	36	(26.08)	63	(38.88)	99	(33)
26-30	45	(32.60)	39	(24.07)	84	(28)
31-35	06	(4.35)	03	(1.85)	09	(03)
36-40	09	(6.52)	09	(5.55)	18	(06)
41-45	15	(10.87)	12	(7.40)	27	(09)
46-50	06	(4.35)	03	(1.85)	09	(03)
51-55	06	(4.35)	03	(1.85)	09	(03)
Total	138	(100)	162	(100)	300	100

Table 2: Frequency distribution of microorganisms in the studied subjects

	Frequency	
Organisms	N	(%)
Bacteria Only	52	(17.33)
Bacteria and Malaria Parasite	23	(7.66)
Malaria Parasite only	211	(70.33)
No Organism	14	(4.66)
Total	300	(100.0)

Table 3: Prevalence of bacterial isolates from blood of the studied subjects

	Total	
Bacteria	N	(%)
Klebsiella pneumonia	9.0	(12.0)
Pseudomonas aeruginosa	18.0	(24.0)
Proteus vulgaris	6.0	(8.0)
Proteus mirabilis	6.0	(8.0)
Serratia mascence	3.0	(4.0)
Salmonella typhi	24.0	(32.0)
Staphylococcus aureus	9.0	(12.0)
Total	75	100

DISCUSSION

Pyrexia can result in considerable malaise, dehydration and anorexia. Therefore, clinicians must decide in each case whether NSAIDs could be beneficial [12]. In Africa including Nigeria, not much has been recorded on pyrexia of undetermined origin. In this study, the age groups 26-30 and 21-25 were the most affected by pyrexia of undetermined origin for both male and female. This observation is similar to that reported by Mir *et al.* [13] where it was found that the age group 16-40 accounted for 53.33% of both male and female affected by pyrexia of unknown origin. They further stressed that most of the cases of PUO were due to infectious diseases.

Similar results were reported by various studies from Asia and the Middle East [14, 15]. Infection still remains the most common cause of classical PUO all over the world even though the demographics vary from region to region [16].

In this study, the highest percentage of the most affected age groups are still dependent on their parents for a living and are relatively poor, live in a crowded environment with inadequate sanitation which might have triggers mosquito bite and subsequently malaria. In our series of 300 cases of classical PUO, that were observed over a period of two years, the diagnosis of a specific cause was established in 286 cases (95.34%), with 14 cases (4.66%) remained undiagnosed. Of the diagnosed subjects, pyrexia was mostly due to malaria 211(70.33). 52(17.33) of the studied subjects had bacteremia while 23 (7.66) of the subjects had both bacteremia and malaria. The presence of malaria in our study as the most prominent cause of pyrexia of undetermined origin in this study is not surprising as malaria has been named a morbid disease of tropical countries, like, India, Pakistan, Bangladesh including Nigeria and is now of global importance. This is because, it is responsible for 1.5 to 2 million of deaths yearly in the world [17] and three fourth of cases were suffered in India amongst 2.48 million of malarial cases of South-East Asia [18].

In tropical countries, where malaria is endemic, it is very essential to differentiate malaria from other viral or bacterial infections by symptoms and signs to prevent future fatal complications, like, cerebral, renal and gastrointestinal [19]. In Nigeria, there are an estimated 100 million malaria cases with over 300,000 deaths per year in Nigeria. This compares with 215,000 deaths per year in Nigeria from HIV/AIDS. Malaria contributes to an estimated 11% of maternal mortality [20]. All cases of malaria observed in this study were caused by *Plasmodium falciparum* and none had complicated malaria. These findings corroborated earlier report from another region [21].

Contrary to most findings in other places of the world, where bacteria were the leading etiological agent of pyrexia of undetermined origin in India [22] and Iran [23], It was uncovered in this study that malaria parasite and specifically *Plasmodium falciparum* was the most predominant species of Plasmodium with frequency occurrence of 70.33 in the blood of the studied subjects.

Bacteremia was the second most frequently seen observation. However, neither tuberculosis nor brucellosis were found despite been widely reported. 23(7.66%) of the subjects showed co-infection of bacteria

and malaria parasite. This is in accordance with report by Were *et al.* [22], who found clinical outcomes of bacteremia in children with *Plasmodium falciparum* infections. In fact, accumulating evidence from sub-Saharan Africa demonstrates that invasive bacterial infections are important concurrent infections in pediatric populations with severe malaria and other childhood illnesses [23-26]. The elevated rate of bacteremia in the studied population may be due to the high prevalence of respiratory and gastrointestinal tract infections, as well as malnutrition, in the study area [27-29].

The prevalence of malaria parasitemia was higher than that of bacteremia. This clearly indicates that malaria parasitemia is mostly responsible for fever of undetermined origin in this locality as reported by Gwer *et al.* [30] while the prevalence rate found in our study (70.33%) is higher than 52.76% reported by by Ehart *et al*. [31]. The difference observed in the two studies could be due to variation in geographical location and types of subjects studied. On the part of bacteremia, distribution percentage found (17.33%) is lower than 44% reported by Khanal *et al.* [32]. The variation observed may not be unconnected to the possibility of some of the subjects already placing themselves on some antibiotics without disclosure and/or differences in sample size as well as subjects themselves. The mixed bacterial and malarial infections prevalence of 7.66% found in this study is lower than that previously reported by Were *et al.* [22] and Ukaga *et al.* [33] which showed prevalence of 35.2 and 11.7% respectively. This may be, because they used patients already confirmed positive to malaria parasitemia.

The most common Gram-positive isolate in the studied subjects was *Staphylococcus aureus*. The results for subjects presenting at the hospital are similar to those of recent investigations showing that *S. aureus* is the most frequent cause of community acquired bacteremia caused by Gram-positive organisms in infants and young children in Nigeria and Mozambique respectively [30-33]. Mehta *et al*. [34] have reported the incidence of 80.96% for Gram negative and 18% for Gram positive which is similar to present findings. Our study revealed that Gram negative bacteria were predominant (88%). In the present study, *Pseudomonas aeruginosa* accounted for 21% of total isolated bacteria, followed by *Salmonella typhi* (17.77%). This observation is contrary to earlier report which stated that *Escherichia coli* is the most common gram negative organism isolated from blood streams infections. In many studies, we observed a gradual but definite rise in isolation frequency of *Pseudomonas aeruginosa* which is of great concern. This bacterium is associated with high degree of resistance to antibiotics. Blood stream infections with *Pseudomonas aeruginosa* have been associated with increased morbidity in some studies. Another significant finding of this study is the isolation of *Salmonella typhi* in 17.77% of the cases. This is in sharp contrast with the report of Uwe *et al*. [35] who reported that *Salmonella typhi* was identified in 100 (69.0%) out of 145 bacterial isolates from blood in Ghana. The species of bacteria recovered from urine samples in this study were *Escherichia coli* (most frequently isolated), followed by *Klebsiella pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Proteus mirabilis and Candida albican.* This agrees with the report of Wammanda *et al.* [36]. It can therefore be concluded based on the results of this study that bacteremia is second only to malaria as the cause of pyrexia of undetermined origin in the studied area.

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