INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY HEALTH SCIENCES
ISSN: 2394 9406

"REVIEW STUDY OF PYREXIA OF UNKNOWN ORIGIN AND RELATED INVESTIGATIONS"

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Abstract:-

Pyrexia of unknown origin (PUO) is a syndrome that has longlytested by the skills of physicians to achieve a diagnosis in affected patients. By definition, patients included in this syndrome will be more difficult to diagnose as they have already resisted classification during baseline investigations[1].And Further , investigation of PUO requires knowledge of many diseases across a range of clinical specialties, as well as knowledge of less commonly used investigative tools. As both society and medicine continue to change, the aetiology and epidemiology of the diseases that cause PUO also change. For these reasons, it is important for physicians to approach PUO in a logical manner, and for the causes and approach to PUO to be continuously reviewed. In this article, we review the aetiology of PUO and the diagnostic strategies that may be used to investigate it.

Key words:-

PUO, etiology, epidemiology, logical manner, diagnosis, syndrome, baseline investigation.

INTRODUCTION :-

Fever of unknown origin (FUO) was first described by Dr. Petersdorf and Dr. Beesom in 1961.[3] FUO was defined as a temperature of 101 degrees Fahrenheit (38.3 degrees Centigrade) or higher with a minimum duration of three weeks without an any diagnosis after an intensive one-week investigation in the hospital. Today, as technology advances allowing for sophisticated outpatient evaluations, the one-week inpatient investigation is no longer required. This activity reviews the cause and presentation of fever of unknown origin and highlights the role of the interprofessional team in its management.

Different subgroups with PUO have been suggested, each requiring different investigative strategies: classical, nosocomial, neutropenic and HIV-related.[4]The causes of PUO can be considered in four categories: infective, inflammatory, neoplastic and miscellaneous. The relative prominence of each category has changed over time, with an increasing proportion of patients who remain undiagnosed, which may be up to 51% of cases. Infectious causes account for 17–35% of cases, inflammatory causes 24–36%, neoplastic causes 10–20% and miscellaneous causes 3–15%. [5]An older multimorbid population, increased global travel, HIV infection, the increase in organ transplantation and immunomodulation for many diseases, evolving diagnostics and changing antimicrobial resistance patterns have all changed the management of patients with PUO.

OBJECTIVES:

- Describe the workup of a patient with a fever of unknown origin.

And .Find out the causes for it.

- Summarize the treatment of patients with fever of unknown origin.
- Review the importance of improving care coordination among inter professional team members to improve outcomes for patients affected by fever of unknown origin.
- Clinical approach

Epidemiology

Epidemiology of fever of unknown origin (FUO) varies based on etiology of fever, age group, geography, environmental exposure, and immune/HIV status. In developing countries, an infectious etiology of FUO is most prevalent whereas, in developed countries, FUO is likely due to non-infectious inflammatory disease.[6]

The diagnostic approach to a patient with PUO should be methodical. A thorough history is essential and will have to go back months or years to yield clues to potential aetiologies for investigation.[7]There is no clear-cut diagnostic approach to fever of unknown origin (FUO). Thorough history with a focus on the most probable etiology based on the patient's symptoms is the key to pinpoint the origin of FUO. Information about previous illnesses, localizing symptoms, alcohol intake, home medications, occupational exposures, pets, travel, and familial disorders should not be overlooked. Constellation of patient-reported symptoms should help providers narrow down

the etiology of the etiologic category of fevers as each of these has clinical hallmarks. For example, if a patient presents with B-symptoms, early satiety, and significant weight loss, the provider should pursue a malignancy workup. On the other hand, if a patient presents with rigors, an infectious etiology should be considered, while joint involvement is a hallmark of rheumatologic disorders. [8]

Important Aspects of History

- Family history
- Immunization history
- Dental history
- Occupational history
- Travel history
- Nutrition and weight history
- Drug history (over-the-counter medications, illicit substances)
- Sexual history
- Recreational habits
- Animal contacts
- Surgery, trauma, or procedures

Fever Patterns

Importantly, fevers should be verified in a clinical setting, and fever patterns should be analyzed. Fever pattern analysis can provide additional clues to specific infectious culprits.

- Tertian or quartan fever in prolonged malaria (occurring every third or fourth day)
- Undulant fever in brucellosis (fevers and sweats in the evening, resolving by morning)
- Tick-borne relapsing fever in borreliosis (week-long fevers with week-long remissions)
- Pel-Ebstein fever in Hodgkin disease (week-long high fevers with week-long remissions)
- Periodic fevers in cyclic neutropenia
- Double quotidian fever (two fever spikes a day) in adult Still disease, malaria, and typhoid

As well as a detailed examination of the respiratory, cardiovascular and alimentary systems one must pay special attention to other important sources of fever. This includes: full examination of the spine and joints; top-to-toe examination of the skin for rashes, ulcers, scars, bites, pressure areas and abnormalities of the hair and nails; review of dentition; temporal arteries; fundoscopy; breast examination, particularly in women; and pelvic or rectal examination including the prostate in men. Any implant is a potential site of infection and must be examined if possible, including prosthetic joints, pacemakers, pacemaker wires, central or peripheral vascular lines, shunts, grafts and meshes.

Etiology

The causes of fever of unknown origin (FUO) are often common conditions presenting atypically. The list of causes is extensive, and it is divided into broader categories, such as infection, noninfectious inflammatory conditions, malignancies, and miscellaneous.

Noninfectious Inflammatory Causes of FUO

- Giant cell (temporal) arteritis
- Adult Still disease (juvenile rheumatoid arthritis)
- Systemic lupus erythematosus (SLE)
- Periarteritisnodosa/microscopic polyangiitis (PAN/MPA)
- Rheumatoid arthritis (RA)
- Antiphospholipid syndrome (APS)
- Gout
- Pseudogout
- Behçet disease
- Sarcoidosis
- Felty syndrome
- Takayasu arteritis
- Kikuchi disease
- Periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome

Infectious Causes of FUO

- Tuberculosis (TB)
- Q fever
- Brucellosis
- HIV infection
- Abdominopelvic abscesses
- Cat scratch disease (CSD)
- Epstein-Barr virus (EBV) infection
- Cytomegalovirus (CMV) infection
- Enteric (typhoid) fever
- Toxoplasmosis
- Extrapulmonary TB
- Organ-based infectious causes of FUO:
    - Subacute bacterial endocarditis (SBE)
    - Chronic sinusitis/mastoiditis
    - Chronic prostatitis
    - Discitis
    - Vascular graft infections
    - Whipple disease
    - MulticentricCastleman disease (MCD)
    - Cholecystitis
    - Lymphogranulomavenereum (LGV)
- Tickborne infections:
    - Babesiosis, Ehrlichiosis
    - Anaplasmosis
    - Tickborne relapsing fever (rodent-infested cabins)
- Regional infections:
    - Histoplasmosis
    - Coccidioidomycosis
    - Leptospirosis
    - Visceral leishmaniasis
    - Rat-bite fever
    - Louse-borne relapsing fever

Malignant and Neoplastic Causes of FUO

- Lymphoma
- Renal cell carcinoma
- Myeloproliferative disorder
- Acute myelogenous leukemia
- Multiple myeloma
- Breast/liver/pancreatic/colon cancer
- Atrial myxoma
- Metastases to brain/liver
- Malignant histiocytosis

Miscellaneous Causes of FUO

- Cirrhosis (due to portal endotoxins)
- Drug fever
- Thyroiditis

- Crohn disease
- Pulmonary emboli
- Hypothalamic syndrome
- Familial periodic fever syndromes
- Cyclic neutropenia
- Factitiou

Evaluation (related investigation):-

When working up the differential diagnosis for FUO, it is important to remember that the cause is more likely a subtle or atypical manifestation of a common disease rather than a rare disease. Diagnosing a cause of FUO can be a very difficult task and requires repeated diligent and thorough history taking along with a complete physical examination.

Non-invasive Tests

Initial diagnostic testing should include:

- Complete blood count with differential
- Complete metabolic panel
- Urine analysis with microscopy and urine culture
- Three sets of blood cultures (from different sites, several hours apart, and prior to initiation of antibiotic therapy)
- Chest radiograph
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Lactate dehydrogenase (LDH)
- Creatinine phosphokinase
- ANA(antinuclear antibody)
- Rheumatoid factor
- Cytomegalovirus IgM/PCR
- Heterophile antibody test
- Tuberculin skin test or interferon-gamma release assay
- HIV immunoassay
- CT scan of the abdomen
- CT scan of the chest
- Cardiac echocardiography can be helpful if culture-negative endocarditis or atrial myxoma is suspected.

To diagnose FUO, the non-invasive testing outlined above should have been inconclusive. At this point, a clinician should exclude surreptitious manipulation of the thermometer and analyze patients' medication lists to evaluate for drug-induced fevers.[9]

History	Examination	Investigation
Drenching night sweats	Measurement of fever	Full blood count
Weight loss	Lymphadenopathy	Liver function tests
Headache	Scalp tenderness	ESR, CRP
Haemoptysis	Hepatosplenomegaly	HBV, HCV, HIV
Altered bowel habits	Cardiac murmurs	Urine cultures
Occupation	Respiratory auscultation	Blood cultures
Travel	Rashes	ANA, RF
Recreational activities		EPG
Injecting drug use		Chest X-ray
Medications		Abdominal CT
		Echocardiog

History	Examination	Investigation
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Disease	Pathogen	Vector/risk factor
Dengue fever	Dengue virus†	*Aedesaegyti* mosquito
Barmah Forest virus	Barmah Forest virus†	Multiple mosquito species
Ross River fever	Ross River virus†	
Q fever	*Coxiella burnetii* ‡	Livestock, esp. abattoir workers, can be occult exposure and many animals implicated
Histoplasmosis	*Histoplasmacapsulatum* †	Bat and bird droppings esp. caves and chicken coups
Scrub typhus	*Orientiatsutsugamushi*	Chiggers (mites)
Queensland tick typhus	*Rickettsia australis*	*Ixodesholocyclus* ticks
Flinders island spotted fever		
Murine typhus	*Rickettsia typhi*	Rat fleas (*Xenopsyllacheopis*)
Brucellosis	*Brucella suis*	Feral pigs, usually hunters 11,12,13
Psittacosis	*Chlamydia psittaci*	

If the diagnosis is not obtained with first-line investigations, then more invasive investigations can be considered. Traditionally, CT scanning of the chest, abdomen and pelvis, with the administration of intravenous contrast, has been the imaging modality of choice;however, recent evidence suggests a higher sensitivity with the combination of CT with fludeoxyglucose positron emission tomography (FDG-PET/CT). This technique allows the matching of inflammatory lesions with a precise anatomical location.. In case the cost is prohibitive, a CT scan with intravenous contrast would be appropriate, and many physicians have found gallium scans to be a useful diagnostic tool.More invasive diagnostics, such as bone marrow biopsy, temporal artery biopsy and transoesophageal biopsy (TOE), should not be performed routinely and only be performed if indicated by previous history,

examination or investigations. Factors, such as suspicion of haematological malignancy, thrombocytopaenia and anaemia, will increase the likelihood of a bone marrow biopsy being a useful investigation tool. There is limited evidence regarding the use of TOE in PUO; however, the DUKE criteria, which includes echocardiography, have been evaluated and found to be highly specific. Given this, it is recommended to perform echocardiography when there is a possibility of culture-negative endocarditis.Transoesophageal echocardiography has a higher sensitivity than transthoracic echocardiography and is the preferred method.

Condition	Key features	Investigations
Infective endocarditis	New cardiac murmur	Blood cultures
	Splinter haemorrhages	Echocardiography
	History of valvular pathology or injecting drug use	Serology for Brucella, Bartonella, Q fever
Disseminated tuberculosis	Weight loss	Chest X-ray
	Drenching night sweats	Mycobacterial blood cultures
	Cough	Sputum cultures for acid-fast bacilli
	Travel or time spent in endemic region	HIV test
Central nervous system tuberculosis	Headaches	Cerebral MRI or CT scan with contrast
	Reduced level of consciousness	Lumbar puncture
Giant cell arteritis (temporal arteritis)	Unilateral headache	ESR

Most patients with PUO will have experienced symptoms for a considerable amount of time and seen multiple doctors, and their faith in their medical attendants can be tested. Appropriate counselling of the patient is of paramount importance to ensure that they understand the process of investigating PUO, especially that in recent times, half the patients will remain undiagnosed.[14]In particular, if no diagnosis is able to be obtained, and there are no 'red flag'

symptoms, signs or investigations, it is important to emphasise that mortality is low.[15]

CONCLUSION:-

PUO is clinical challenge despite greater understanding of the diseases responsible and increased access to diagnostic tests. New technologies, such as FDG-PET, show promise to aid in diagnosis; however, detailed history and examination remain the most important steps in achieving a diagnosis for the patient and guiding further investigation. Whilst the initial literature utilised an inpatient approach to investigation, the increasing ease of access to investigations and low short-term mortality of PUO makes outpatient management not only possible but recommended except in cases of severe illness. The principles originally espoused remain useful today, particularly that the investigations most likely to yield a diagnosis should be performed early and that therapeutic trials are unlikely to be helpful. Whilst this review is designed to give an overview of PUO, there are many excellent reference materials with more comprehensive information.

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