# Fever of unknown origin: A rheumatologic perspective

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## Abstract

Fever of Unknown Origin (FUO) is a syndrome defined by persistent fevers above 38.3$^0$C that lasts for longer than 3 weeks with no obvious source. It usually poses a diagnostic challenge to the clinician.

We describe a case of FUO in a young male adult who was treated several times with antibiotics and anti-malarial with no resolution of symptoms. A diagnosis of Adult Onset Still's Disease (AOSD) was made after thorough investigation. A methylprednisolone pulse therapy relieved the fevers and maintenance therapy continued with methotrexate.

Adult Onset Still's Disease is a multi-systemic inflammatory disorder that can manifest as FUO and should be suspected if the fever does not respond to therapy.

**Key words:** Adult Onset Still's Disease, Fever of unknown origin

## Introduction

Fever of Unknown Origin (FUO) is a syndrome defined by persistent fevers above 38.3$^0$C and present for longer than 3 months[1]. The differentials for FUO is vast and can be grouped as malignancies, infections and autoimmune conditions[1]. It therefore requires an extensive laboratory and radiological work up. Adult Onset Still's Disease is a rare multi-systemic disorder that manifests in 5 to 10% of patients with FUO[2]. Some of the diagnostic criteria's used are Yamaguchi, Cush, Calabro and Fautrel, however none has been validated in Africa. High ferritin levels has been associated with AOSD[3]. We describe a case of AOSD that manifested as FUO and did not fully fulfil the Yamaguchi criteria but had elevated ferritin levels.

## Case report

A 16 year old school going African male presented with 1 episode of tonic clonic convulsions that lasted 5-7 minutes and a 3 month history of fever on and off that was relieved by paracetamol. There was positive history of 25kg weight loss in the past three months despite good appetite and food intake. He denied any history of diarrhoea, vomiting, cough, joint pains, rash and oral ulcers. There was no history of contact with person suffering from TB however he did come from a TB endemic zone. Systemic enquiry did not reveal anything significant.

Prior to presentation he had been seen at a peripheral clinic and completed a full course of anti-malarial as well as cefixime 2g bd. He was also started on iron supplementation for anaemia. His past medical and family social history were non-contributory. On physical examination he was febrile with a temperature of 38.8$^0$C, pulse rate of 99 beats per min and a blood pressure of 106/62. He had no lymphadenopathy present. Abdominal exam revealed a hepatosplenomegaly. Cardiovascular, respiratory and neurological exam were normal.

His initial work up revealed a microcytic hypochromic anaemia (hb 12.2g/dl, MCV 74.4fl, MCH 24.8 pg), WBC 4.89 x 10$^9$ with a neutrophils of 36%. His kidney function test was normal while transaminases were slightly elevated (ALT 50U/L, AST 65U/L,YGT 109 U/L). CRP was elevated at 41.6 mg/L, ESR elevated 27mm/hr and procalcitonin was normal at 0.83 ng/ml. Thorough screening for infection was negative (Salmonella typhi antigen, multiple blood and urine cultures, urinary lipoarabinomannan, VDRL, tropical fever PCR, HIV, CMV and EBV) TB Gold Quantiferon was indeterminate. Autoimmune screening tests were also negative (ANA, ENA panel, p-ANCA, c-ANCA, anti dSDNA and complement levels). Serum ferritin was elevated at 743 ng/ml.

Other tests included: sickling test negative, uric acid and LDH levels normal. Peripheral smear revealed a microcytic hypochromic picture. Radiological examinations were as follows: 2D ECHO, CXR, ECG and MRI brain were normal. Abdomino-pelvic ultrasound revealed

a hepatosplenomegaly and CT chest showed bilateral multiple pulmonary nodules with no hilar or mediastinal lymphadenopathy. Initially the patient received empirical antibiotics meropenem and azithromycin for 4 days with no improvement in symptoms and thus were stopped. Attempts to control fever with paracetamol were unsuccessful.

A rheumatologist review was done and a diagnosis of probable Adult Onset Still's Disease was made and recommended methylprednisolone pulse therapy of 500mg intravenous for 3 days. There was complete resolution of fevers after the first dose of methylprednisolone. Serum ferritin levels after the pulse therapy dropped to 207.9ng/ml. He was then initiated on oral prednisolone 15mg twice a day for 1 week with gradual tapering over 2 months. Steroid sparing therapy was initiated with methotrexate 10mg once a week and folic acid 5mg daily.

## Discussion

Adult Onset Still's Disease (AOSD) is rare multi-systemic disorder of unknown aetiology[2]. It affects 1–1.5 cases per 100, 000 people[2,4]. Its prevalence in Africa is unknown with very little epidemiological data available. A few African case reports have been published from Nigeria[4], Gabon[5], Senegal[6] and Kenya[3], the patients age ranged from 12 to 48 years[2-4]. Some studies suggest a bimodal peak at ages 15-25 and 36-46 years[7]. It affects both genders but has a higher incidence in women[8].

The exact pathogenesis is poorly understood. Studies suggest an association between AOSD and HLA antigens, viral and bacterial pathogens as well as environmental factors[2]. Innate immune mechanism is activated with elevated levels of inflammatory markers such as IL-1, IL-18, IL-6 and TNF- $\alpha$[2,4].

The most common presentations are fever and arthralgia but other symptoms include rash, sore throat and myalgia[2]. Rare presentations include lymphadenopathy, hepatosplenomegaly, pleurisy, pericarditis and abdominal pain[2,9]. It could also manifest as fever of unknown origin without any other accompanying symptoms[8], this was the case with our patient.

Neurological manifestations are rare, however, some cases have been reported of encephalitis and aseptic meningitis[10,11]. Our patient presented with convulsions but we were unable to fully rule out central nervous system involvement without a consent for a lumbar puncture. Serum ferritin five times the upper limits of normal has 80% sensitivity and 46% specificity in diagnosing AOSD[4]. Glycosylated ferritin levels are decreased and combined with ferritin levels increases sensitivity and specificity compared to either test alone[12]. In this case, the ferritin levels were elevated 1.5 times the normal upper limit. Glycosylated ferritin levels is unavailable in our facility as well as many parts of Africa.The Yamaguchi, Cush, Calabroand Fautrel are the diagnostic criteria used with the first being the most sensitive and commonly used[13,14]. These criteria have not been validated in Africa. The Yamaguchi criteria requires at least 5 to be fulfilled of which 2 must be major[13].

*Major criteria are as follows*: Fever $\geq$ 39°C for at least a week; Arthralgia or arthritis for at least 2 weeks; Non-pruritic salmon colored rash; Leukocytosis $\geq$ 10,000/mm$^3$ with neutrophil predominance.

*Minor criteria are as follows:* Sore throat or pharyngitis; Lymphadenopathy; Hepatomegaly or splenomegaly; Abnormal liver function tests; Negative tests for RF and ANA.

Our patient fulfilled only 1 major and 3 minor criteria. Still's rash though part of a major criteria may not be present in all cases. A Kenyan study done by Oyoo *et al*[15] only one of 68 children with JIA had the presence of still's rash. Salmon coloured rash may not be very visible on dark pigmented skin. The Fautrels criteria requires glycosylated ferritin level[11] and its use is therefore limited in Africa due to availability of the test.

Non-Steroidal Anti Inflammatory have no role in AOSD with only 16% remission rates and higher incidence of adverse events[16]. Steroids are the mainstay of treatment and control symptoms in 60% of cases[2,16]. New evidence supports the use of biologics in the early course of diseases e.g methotrexate, anakinra and tocilizumab[16]. Our patient received methylprednisolone pulse therapy with immediate resolution of fevers. Further treatment with tocilizumab as maintainance therapy was not possible due to financial constraints therefore methotrexate was the affordable steroid sparing option. The American College of Rheumatology recommends screening for latent tuberculosis before initiating treatment. During therapy continuous screening is recommended for high risk patients. Our patient came from a TB endemic zone and thus a clinical decision to start him on 3 months rifinah prophylaxis was made.

## Conclusion

AOSD is rare and one should have a high index of suspicion when dealing with fevers of unknown origin in young adults.

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