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Fever of unknown origin − diagnostic methods in a European developing country

Nejasno febrilno stanje – dijagnostičke metode u evropskoj zemlji u razvoju

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Abstract

Background/Aim. Fewer of unknown origin (FUO) remains amongst the most difficult diagnostic dilemmas in contemporary medicine. The aim of this study was to determine the causes of FUO and to identify the methods of diagnosis in patients with FUO in a tertiary care setting in the Republic of Macedonia. **Methods.** Retrospectively histories of 123 immunocompetent patients older than 14 years with classical FUO that had been examined at the University Hospital for Infectious Diseases and Febrile Conditions in the city of Skopje, during the period 2006−2012 were evaluated. FUO was defined as axillary fever of ≥ 37.5°C on several occasions, fever duration of more than 21 days and failure to reach the diagnosis after the initial diagnostic workup comprised of several defined basic investigations. **Results.** Infections were the cause of FUO in 51 (41.5%) of the patients, followed by non-infective inflammatory disorders (NIID) in 28 (22.8%), miscellaneous in 12 (9.7%) and neoplasm in 11 (8.9%) of the patients. Twenty one of the patients (17.1%) remained undiagnosed. The most common causes for FUO were visceral leishmaniasis, abscesses, urinary tract infections, subacute endocarditis, *polymyalgia rheumatica* and adult onset of Still disease. The final diagnosis was reached with histology in 24 (23.5%), imaging and endoscopic procedures in 21 (20.6%), clinical course and empiric therapy response in 20 (19.6%), serology in 18 (17.6%) and cultures in 16 (15.7%) of the cases. **Conclusion.** In the Republic of Macedonia infections are the leading cause of FUO, predominately visceral leishmaniasis. In the future in patients with prolonged fever, physicians should think more often of this disease, as well as of the possibility of atypical presentation of the common classical causes of FUO.

Key words:
fever; infection; diagnosis; diagnosis, differential; leishmaniasis, visceral; macedonia.

Apstrakt

Uvod/Cilj. Nejasno febrilno stanje (*fever of unknown origin* − FUO) ostaje među najvećim dilemama u dijagnostici savremene medicine. Cilj ovog rada bio je da se prikažu uzroci FUO i da se definišu metode kojima je postavljena dijagnoza kod ovih bolesnika u tercijernoj medicinskoj ustanovi u Republici Makedoniji. **Metode.** Retrospektivno su proučavane istorije bolesti 123 imunokompetentna bolesnika starija od 14 godina sa klasičnim FUO koji su bili ispitivani na Univerzitetskoj klinici za infektivne bolesti i febrilna stanja u Skoplju, u periodu 2006−2012. godine. FUO je bila definisana kao aksilarna temperatura ≥ 37,5°C u nekoliko navrata, trajanja dužeg od 21 dana i nepostavljanje dijagnoze posle inicijalnog dijagnostičkog pristupa sastavljenog od nekoliko definisanih ispitivanja. **Rezultati.** Infekcije su bile razlog za FUO kod 51 (41,5%) bolesnika, praćene neinfektivnim inflamatornim bolestima kod 28 (22,8%), raznim drugim stanjima kod 12 (9,7%) i neoplazmama kod 11 (8,9%). Kod 21 (17,1%) bolesnika razlog za FUO nije bio pronađen. Najćešći razlozi za FUO bili su visceralna lajšmanioza, apscesi, infekcije urinarnog sistema, subakutni endokarditis, reumatska polimijalgija kao i Stilova bolest. Krajnja dijagnoza bazirala se na histologiji kod 24 (23,5%), radiološkim i endoskopskim procedurama kod 21 (20,6%), kliničkom toku i odgovoru na empirijsku terapiju kod 20 (19,6%), serologiji kod 18 (17,6%) i kulturama kod 16 (15,7%) bolesnika. **Zaključak.** U Republici Makedoniji infekcije predstavljaju vodeći uzrok FUO, u prvom redu visceralna lajšmanioza. U budućnosti, kod bolesnika sa FUO lekari bi trebalo češće da misle na ovu bolest kao i na mogućnost za atipičnu prezentaciju uobičajenih klasičnih bolesti koje izazivaju FUO.

Ključne reči:
telesna temperatura; infekcija; dijagnoza; dijagnoza, diferencijalna; lajšmanioza, visceralna; makedonija.

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Introduction

Fewer of unknown origin (FUO) remains amongst the most difficult diagnostic dilemmas in contemporary medicine [1, 2]. Nowadays, there are more than 200 known causes of FUO [3–5], but their true incidence and prevalence are unknown [6]. The etiologic spectrum of diseases that cause FUO is determined by different factors like geographic conditions, economic characteristics of the country, the time period when the study was done, whether the study was prospective or retrospective one, inclusion and exclusion criteria, availability and quality of diagnostic methods, the increasing number of intravenous drug users, travelers, as well as by the development of new diagnostic tools, new vaccines and new antimicrobial and immunomodulating agents [7–10].

The physicians that manage this category of patients encounter a lot of difficulties: the possibility to conduct investigations in wrong direction due to the accentuation of some or disregarding other potential diagnostic clues (PDCs), unintentional omission of appropriate diagnostic techniques, or simply not recognizing the disease as a result of its atypical clinical presentation. The always present probability for worsening the patient's health due to delay of empirical treatment, as well as the possibility to harm the patient with certain investigations or the used drugs, make the management of this kind of patients even more complex [1, 11].

Concerning FUO in the Republic of Macedonia, there is a lack of epidemiological and clinical data, and this study aimed to present the causes of classic FUO and to determine the role of diagnostic methods performed in order to reach the diagnosis in this developing country.

Methods

This retrospective study evaluated medical records of 123 immunocompetent patients older than 14 years with non-hospital acquired FUO. The patients were investigated at the University Hospital for Infectious Diseases and Febrile Conditions in the city of Skopje, Republic of Macedonia, during the period January 2006−December 2012. The patients were assessed as inpatients or as outpatients and they were admitted directly, or were transferred from other hospitals. The study was approved by the Medical Faculty Review Board.

The inclusion criteria were: axillary fever of ≥ 37.5°C on several occasions; fever duration of more than 21 days, and failure to reach the diagnosis after the initial diagnostic workup comprising: of detailed medical history which included actual symptoms, their features and duration, previous illnesses, surgical procedures, comorbid conditions, medications, alcohol intake, occupation, social environment, sexual and travel history, hobbies, animal exposure, animal or insect bites, recent contact with persons with similar symptoms, familial disorders; thorough physical examination with special accent on the skin, nails, mucous membranes, lymph nodes, eyes, ears, nose, sinuses, oropharynx, heart, lung, abdomen, extremities, nervous system, temporal arteries, rectum and genital organs; initial laboratory tests − erythrocyte sedimentation rate, C-reactive protein, complete blood count with differential leukocyte formula, glycaemia, blood urea nitrogen, creatinine, sodium, potassium, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, alkaline phosphatase, gamma-glutamyl transpeptidase and urine analysis; other investigations − blood cultures (≥ 2), urine culture, serology for brucellosis, anti HIV test, chest x-ray, electrocardiography, abdominal ultrasonography and tuberculin skin test.

After enrollment, additional advanced evaluation consisted of the systematic approach which included repeated questioning of patients and their close relatives and frequent physical reexamination done by different physicians in order to evaluate changes in the presentation or appearance of new symptoms or signs. At the same time body temperature and heart rate were measured every few hours in the presence of medical personnel, and all unnecessary drugs were discontinued or replaced with more adequate ones. Depending on the actual PDCs the patients were submitted to repetition of some of the initial diagnostic tests, as well as to some of the following second line investigations: biochemical tests − serum protein electrophoresis, fibrinogen, complement, circulating immune complexes, thyroxin and thyroid stimulating hormone, angiotensin-converting enzyme, hemostasis, Bence Jones proteinuria, 24 hours proteinuria, occult blood in feces; anti-nuclear antibody, rheuma factor, anti-deoxy ribonucleic acid antibodies, anti-neutrophil cytoplasmic antibodies, tumor antigen assays (AFP, CEA, PSA, CA 125, CA 72-4, CA 19-9, NSE, CYFRA); microbiological analyses − sputum microscopy and sputum for acid fast bacilli, thick and thin blood smear for malaria; stool, throat, cerebrospinal fluid, pleural fluid, ascitic fluid cultures; serological tests − antistreptolysin-O test, Widal, WDRL; indirect immunofluorescent antibodies (IIF) for visceral leishmaniasis, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella, Coxiella, Rickettsia*; enzyme-linked immunosorbent assay for viral hepatitis, *Toxoplasma, Epstein-Barr* virus, *Cytomegalovirus, Leptospira, Borrelia, Clostridium difficile* toxin in stool; imaging studies − radiography of the paranasal sinuses, teeth, pyelography, craniogram, angiography; ultrasound examination of thyroid gland, heart, kidney, lung, pelvic region, doppler imaging; computed tomography or magnetic resonance imaging of brain, thorax, upper and lower abdomen; scintigraphy with marked leucocytes; invasive procedures and histological examination − bronchoscopy, cystoscopy, gastroscopy, colonoscopy with adequate biopsies, sternal aspiration, bone marrow, liver, lymph node, skin, muscle, and other solid organs biopsy.

Data on age, gender, fever duration prior to inclusion in the study, time from the inclusion in the study to establishing the final diagnosis, and diagnostic methods used for establishing the diagnosis were analyzed. To decide on the definitive diagnostic method we took into consideration biochemistry and hematological analyses, microbiological cultures and smears, serology (microbiological and immunological), imaging techniques, endoscopic procedures, histology, and clinical course and/or empiric therapy response. Interpretation of data and establishing the final diagnosis was made by one of the authors in concordance with at least one other specialist

in infectious diseases, rheumatology, hematology, oncology, or other related specialties.

The causes of FUO were classified into 5 diagnostic categories: infections, neoplasm, non-infective inflammatory disorders (NIID) including connective tissue illnesses, vasculitides and granulomatous disorders, miscellaneous, and non-diagnosed diseases.

Patient's age, fever duration before inclusion in the study and the time from inclusion in the study to establishing the final diagnosis are presented using median and range values. All other parameters are presented as frequencies and percentages.

Results

This retrospective study included 123 patients with the median age 49, range 15−82 years. Sixty four (52%) of the patients were males, and 59 (48%) females. Sixty six (53.6%) of the patients were previously investigated as inpatients in other hospitals. Before their inclusion in the study, all the patients had at least one course of antimicrobial therapy. Fever duration before the inclusion in the study was on the avarage 30 days, range 10−1,440 days. Twenty one (17.1%) of the patients during their first examination in our hospital had fever duration of less than 21 days and this criterion for FUO (fever duration) was fulfilled during investigations after their hospital admittance. As shown in Table 1, infections were the most common causes of FUO, followed by NIID. In the group of infections, visceral leishmaniasis and abscesses were the dominant conditions. There were 7 males and 3 females with visceral leishmaniasis, average age 47, range 23−60 years. In this group of patients fever duration prior to admission was median 30, range 21−90 days. The diagnosis was reached with detection of parasites in material obtained from sternal aspiration in 4 out of 6 examined patients and in the remaining patients with indirect immunofluorescence (IIF) test. IIF test was positive in 9 out of 10 examined patients. In all the patients with visceral leishmaniasis defervescence was reached up to 10 days after beginning of specific treatment with antimonial compounds. In the NIID group the commonest conditions were *polymyalgia rheumatica* and adult onset Still disease. As far as neoplasms are concerned, the metastatic carcinoma of the liver was dominant, and in the group of miscellaneous diseases deep vein phlebothrombosis was the leading cause. However, in 21 (17.1%) of the patients the cause of FUO remained obscure in spite of all investigations and follow-up. This category of the patients composed of 12 females and 9 males with median age of 45, range 18−67 years, prior to inclusion in the study had illness duration of 60 days, range 14 days to 4 years. Fourteen patients were previously investigated in other hospital settings. The duration of the hospital stay was median 21, range 14−60 days. One patient died during the hospital stay, in 9 fever continued to be present at hospital discharge, and in 11 fever resolved during the stay in the hospital (in 4 of them spontaneously, and in 7 with corticosteroid therapy). All of the patients on corticosteroids and those that were discharged with fever were advised to consult specialists of various internal medicine branches.

In cases with the diagnosis, the time from inclusion in the study to establishing the final diagnosis was median 12, range 8−60 days. As shown in Table 2 all of the cited methods had their own contribution to establishing the final diagnosis.

Table 1
Causes of fever of unknown origin (FUO) in 123 patients

Causes	Patient, n (%)
Infections	51 (41.5)
Visceral leishmaniasis	10
Abscess*	10
Urinary tract infection†	6
Subacute endocarditis‡	6
Tuberculosis§	5
Pansinusitis	3
Cytomegalovirus infection	2
Sepsis‖	2
Lyme borreliosis	2
Other¶	5
Non-infective inflammatory disorders	28 (22.8)
Polymyalgia rheumatica	6
Adult onset Still disease	6
Vasculitis	4
Systemic lupus erythematosus	3
Crohn disease	3
Reactive arthritis	3
Other**	3
Neoplasm	11 (8.9)
Haematological disorders††	4
Metastatic adenocarcinoma in the liver	3
Colonic adenocarcinoma	2
Prostatic cancer	1
Leiomyosarcoma	1
Miscellaneous	12 (9.7)
Deep vein phlebothrombosis	5
Subacute thyroiditis	2
Ulcerative colitis	2
Other‡‡	3
Undiagnosed	21 (17.1)

***6 cases with abdominal/pelvic, 2 with dental, 1 with breast and 1 with cervical lymph gland abscess; †Urine culture: *Escherichia* (*E.*) *coli* in 3, *Enterococcus* in 2 and *Proteus mirabilis* in 1 patient; ‡Blood culture: *Staphylococcus* (*S.*) *aureus* in 1, *Enterococcus* in 1, negative in 4 patients; §1 case each with miliaria, tuberculous spondylitis, epididymitis, lymphadenitis, pericarditis; ‖Blood culture: *S. aureus* in 1, *E. coli* in 1 patient; ¶1 case each with leptospirosis, rickettsiosis, *Clostridium difficile*, parvoviral infection and cholecystitits; **1 case each with sarcoidosis, granulomatous hepatitis and erythema nodosum; ††1 case each with Hodgkin lymphoma, non Hodgkin lymphoma, chronic leukemia and myelofibrosis; ‡‡1 case each with lung embolia, cardiac myxoma, and drug fever.**

Table 2

Final diagnostic method in 102 patients with fever of unknown origin (FUO) in whom diagnosis was established

Diagnostic method	Patients n (%)
Biochemistry and hematological analyses	3 (2.9)
Cultures and smears	16 (15.7)
Serology (microbiological and immunological)	18 (17.6)
Imaging, endoscopic and other invasive procedures	21 (20.6)
Histology	24 (23.5)
Clinical course and/or empiric therapy response	20 (19.6)

Discussion

Although there were several attempts to define FUO prior to 1961 [12], this condition has had its true placement with the establishment of criteria by Petersdorf and Beeson [13], which include illness duration of more than 3 weeks, documented temperature higher than 38.3°C on several occasions, and uncertain diagnosis after one week of the hospital diagnostic workup. In 1991 Durack and Street [14] modified the previous definition by replacing the last criterion with the following modification "uncertain diagnosis after 3 days of hospital stay or more than 2 outpatient visits". For some authors this modified definition of FUO is also not satisfactory, considering that it is based on quantitative parameters. Today more current is the tendency to define FUO with the help of qualitative criteria where the time period during which no diagnosis or reasonable diagnostic hypothesis has been made is replaced with a standard initial diagnostic intelligent investigational protocol conducted in or out of a hospital setting [15, 16]. It is recommended that the standard diagnostic protocol should be adapted to the regional epidemiological factors. This was nicely demonstrated in our study by the number of cases with visceral leishmaniasis.

The definition of FUO in this study differs from the classical definition in two criteria. Firstly, in this study the temperature was measured axillary, the method that has deep roots and tradition in this region due to hygiene habits and as a result of having prejudices, especially in male population where rectal measurement of temperature is generally not accepted. Axillary measurement of the temperature is reported in several Japanese studies, although their definition for elevated body temperature varies from ours [17, 18]. The decision we chose for temperature cut off of $\geq 37.5^{\circ}$C was arbitrary – we intended to exclude conditions with habitual hyperthermia and cases with more expressed circadian temperature daily rhythm. Secondly, instead of criterion from 7 or 3 day hospital stay, or more than 2 outpatient visits we used qualitative criteria, considering it to be more objective especially in developing regions, where results from samples taken for examination were received with delay. In addition, it takes more time than usual to obtain the results partly due to objective reasons (some analyses are processed in continuity only in certain days, there is a periodical shortage of reagents, some analyses are done in facilities out of the state etc.), but also due to subjective reasons (indolence in preparation, issuing and collecting the results, absence of priority etc.).

According to numerous literature data, the occurrence of infections, NIID, neoplasms and miscellaneous conditions is 11% [19] to 59% [20, 21], 2% [22] to 38% [23], 6% [24, 25] to 31% [11, 26] and 2% [20, 23] to 22% [27], respectively. The proportion of undiagnosed cases ranges from 5% [26, 28] to 53% [3, 29]. This study similar to others conducted in university clinical centers in developing countries, as well as in secondary hospital care centers in developed countries shows the predominance of infections compared to other causes of FUO [30]. In our series the highest frequency was found for visceral leishmaniasis, an autochthonic disease in our region, but yet rarely thought of, and until recently with sparse diagnostic possibilities. Visceral leishmaniasis as a cause for FUO has been reported in other series as well [7, 20, 31, 32], but not as a predominant cause. From the abundance of other infective causes, dominant were abscesses (intra-abdominal but extra-abdominal as well), urinary tract infections (UTI), subacute endocarditis and extrapulmonary tuberculosis, similarly seen in another studies [9, 20, 33, 34]. A rather high frequency of bacterial infections such as abscesses, UTI and endocarditis can be ascribed to the all too common practice of repeatedly prescribing antibiotics to patients with prolonged fever. Interestingly, in our study there were no cases with human brucellosis as a cause of FUO, something that has been mentioned by other authors [7, 35, 36]. Possibly this is due to the fact that brucellosis, predominantly an endemic disease in this region [37], is often thought of by doctors and patients, as well. From non-infective diseases there was the marked occurrence of *polymyalgia rheumatica*, adult onset Still disease, haematological malignancies and deep vein phlebothrombosis, which were similarly reported in other studies [9, 17, 19, 29, 32, 34, 38].

Having in mind that we did not perform some of the sophisticated diagnostic tests (positron emission tomography – PET scan, genetic investigations, polymerase choin reaction – PCR, fungal diagnostic, temporal artery biopsy), and that all of the patients had prior empirical antimicrobial treatment, the percentage of cases without diagnosis, is comparable to the findings in other studies [24, 39–42]. This may be due to the spectrum of diseases that cause FUO in this region, the fact that half of the patients sought medical help for the first time, and that in some cases we accepted the probable diagnosis as a definite one, with special accent towards diagnostic meaning of clinical course and /or empiric therapy response.

In this study during advanced investigation no algorithms were used [5, 43–45] and to all the patients we had individualized approach. Also, the choice for investigations undertaken was based on PDCs, personal physicians' intuition and experience, but also on the availability and cost of the diagnostic investigations, a fact that is economically justified in areas with limited material resources and technologic potentials. At the same time invasive diagnostic tests were left as an ultimate option when no result was obtained with any of the other previously done investigations which would help solve the case, or when deterioration of the condition was expected. Histology had a leading role in reaching a diagnosis in cases with neoplasms, but also in some other diseases (inflammatory bowel diseases, vasculitis, and tuberculosis). Clinical course and empiric therapy were of special significance, especially in adult onset Still disease, *polymialgia rheumatica*, reactive arthritis and some of the miscellaneous disorders, while in cases of infections microbiological cultures, serological tests and imaging techniques were of special aid. Also, imaging and endoscopic techniques had helped in localization of some of the lesions and in subsequent histological examination. There is a great diversity in the literature considering the definitive diagnostic steps regarding the causes for FUO, available resources in the hospital in question, the interpretation of the results, used definitions and some regional specifics [19, 20, 23, 34, 46–48].

Conclusion

In conclusion, our study showed that in tertiary care hospitals in our country infections are the leading cause of FUO. In the forthcoming period in patients with FUO special concern should be paid to visceral leishmaniasis, abscesses, UTI, subacute endocarditis and tuberculosis, generating the clinical suspicion more often and aiming to improve the available techniques in order to achieve the final diagnosis more quickly. Our findings stress the importance of leishmaniasis, too often considered a tropical disease, as a cause of FUO in travelers visiting these parts of Europe. The great importance that clinical approach has in making the diagnosis of FUO should not marginalize the tendency towards new medical achievements and attempts for introducing new modern diagnostic procedures in order to help solve the diagnosis in some of the cases.

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