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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

The prevalence of vector-borne diseases among patients with fever of unknown origin in a Bulgarian hospital*

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2016, 33(5):656–660

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OBJECTIVE **Fever of unknown origin (FUO) is a puzzling condition. The causes of FUO can be classified in five groups: infections, neoplasia, non-infectious inflammatory diseases, miscellaneous and undiagnosed causes. Vector-borne diseases are important emerging illnesses globally. The aim of this study was to estimate their prevalence and to describe the clinical and laboratory features of patients with vector-borne diseases presenting as FUO.** METHOD **Retrospective analysis was made of the characteristics of 78 patients with febrile syndrome investigated over a period of 4 years at the Department of Infectious Diseases of the Military Medical Academy (Sofia, Bulgaria). All patients underwent a thorough medical history, physical examination and laboratory investigations and the final diagnosis was based on clinical, epidemiological and laboratory data.** RESULTS **The modified Petersdorf-Beeson criteria for FUO were fulfilled by 54 of the patients. A definitive diagnosis was made in 45 and infectious diseases were established in 32 (59.3%) cases. Vector-borne diseases were identified in 10 patients. The diagnosis was determined in 7 as Rickettsioses (*R. conorii* 2/10 and *C. burnetii* 5/10), co-infection with *C. burnetii* and *C. pneumoniae* in one, and Lyme disease in two patients.** CONCLUSIONS **The leading cause of FUO among the Bulgarian population is infectious diseases, in agreement with other published data from South-East Europe. Among infections, the illnesses caused by arthropod-transmitted disease are not rare: 31.3% of all infections. Explanations for these results include the geographical location, climate and level of economic development.**

Συχνότητα νοσημάτων μέσω ενδιάμεσου ξενιστή σε ασθενείς με πυρετό άγνωστης αιτίας σε ένα βουλγαρικό νοσοκομείο

Περίληψη στο τέλος του άρθρου

Key words

Fever
Frequency
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Pyrexia or fever of unknown origin (FUO) is one of the most interesting and puzzling conditions in clinical medicine. The search for the cause of prolonged fever is challenging. The general medical knowledge about FUO dates from 1961, when a definition of this condition was given by Petersdorf and Beeson.[1] The inclusion criteria they proposed were: (a) Fever of higher than 38.3 °C on at least three occasions; (b) duration of fever of at least three weeks; (c) the diagnosis uncertain after one week of hospital investigation.[1] Later this definition was modified and the condition was divided into (a) classical FUO, (b) nosocomial FUO and (c) immune-deficient FUO, and (d) HIV-related FUO.[2] The causes of prolonged fever are classified in 5: (a) Infections, (b) neoplasia, (c) non-infectious inflammatory diseases (NIID), (d) miscellaneous, and (e) undiagnosed causes.[1–4] The distribution of causes is influenced by scientific-technical progress, medical knowledge, the economic and social development of a region and, not least, the geographical region and its climatic features.[5,6] Infectious diseases are the most common category as a cause of FUO, globally.[5–9] The most frequent infections causing FUO are tuberculosis, abscesses and endocarditis.[6,10] Illnesses caused by vector-borne transmission are rare, with varying distribution depending on the climate

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and geographical characteristics of the area and the biology of the vectors. Bulgaria is a European country, but it is located in the south-east part of Europe and influenced by the Mediterranean climate and has special endemic diseases and a variety of vectors for disease transmission. Because of these specific features, we decided to evaluate the prevalence of vector-borne disease among cases of FUO in Bulgaria. The aim was to analyze the clinical and laboratory characteristics of vector-borne diseases as causes of FUO and to discuss the prevalence of these transmitted illnesses among patients with prolonged fever.

MATERIAL AND METHOD

A retrospective study was made of data covering 4 years (2006–2010) at the Department of Infectious Diseases of the Military Medical Academy (Sofia, Bulgaria). The records of patients with prolonged febrile syndrome were analyzed. The inclusion criteria for the study were those of the modified definition of FUO: (a) Fever of higher than 38.3 °C on at least three occasions; (b) duration of fever of at least three weeks and (c) the diagnosis uncertain after three outpatient visits or after three days of intensive hospital investigations.[2] A thorough medical history was taken and physical examination was made of all patients and laboratory investigations were gradually applied. The final diagnoses were grouped into the known and widespread groups of infections, neoplasms, non-infectious inflammatory diseases, miscellaneous, and undiagnosed. Among the infections, detailed analysis was made of the clinical-laboratory parameters of the cases with vector-borne diseases and the findings were compared with publications from other countries. The definition of vector-borne diseases of the World Health Organization (WHO) was used.[11] The definitive diagnosis was based on clinical, epidemiological and laboratory data, whereas for etiological diagnosis traditional culture methods, molecular biology and serological tests were applied.

Statistical analysis

Analysis was performed using Excel 2007 and the Statistical Package for Social Sciences (SPSS Statistics), version 19.0 (Chicago, IL, USA). A p-value of <0.05 was considered significant. The parameters of the laboratory results were calculated as mean ±SD.

RESULTS

During the 4-year study period 2006–2010, 78 patients with prolonged febrile syndrome were hospitalized in the department, of whom 54 met the inclusion criteria for FUO and a definitive diagnosis was made in 45. The distribution by causes was the following: infections (32 cases), neoplasia (2 cases), NIID (8 cases), miscellaneous (3 cases), and there were 9 undiagnosed cases. The infections (59.3%) were the prevailing diseases among the cases with FUO. The etiological distribution of infections was: 10 cases of vector-borne diseases, 8 cases of respiratory infection, 2 cases of co-infection with a respiratory specific pathogen and a hepatotropic virus (HCV and EBV, respectively), 5 cases of gastrointestinal infection caused by a specific pathogen, 5 cases of general infection and 2 cases of parasitological illness. The vector-borne diseases identified were: Q fever in 5 patients, Lyme disease in 2, Mediterranean fever in 2 and co-infection with *C. burnetii* and *C. pneumoniae* in one woman. The sex distribution was equal, 5 men and 5 women, indicating that both genders are involved in agricultural work or hiking in the countryside, and have equal exposure to arthropods. The age of the patients was variable (tab. 1), the youngest patient being 18 years and the oldest 70 years, and every age group being affected by

Table 1. Clinical manifestations and physical findings in patients with vector-borne diseases (n=10) in a population with fever of unknown origin (FUO) (n=54).

Variables		**Parameter**
Years (mean±SD)		45.4±18.7
Hospital days (mean±SD)		8.8±2.7
Fever days (mean±SD)		89.9±109.8
Clinical manifestations/history		**%**
Animal contact	Of all patients	1.9
	Of all infections	3.1
Arthralgia	Of all patients	7.4
	Of all infections	12.5
Fatigue	Of all patients	14.8
	Of all infections	25.0
Insect bites	Of all patients	3.7
	Of all infections	6.3
Skin rash	Of all patients	5.6
	Of all infections	9.4
Travel abroad	Of all patients	1.9
	Of all infections	3.1
Physical findings		**%**
Arthritis	Of all patients	1.9
	Of all infections	3.1
Hepatomegaly	Of all patients	3.7
	Of all infections	6.3
Skin rash	Of all patients	1.9
	Of all infections	3.1
Splenomegaly	Of all patients	1.9
	Of all infections	3.1

vector-borne diseases. The leading complaints were fever, fatigue and arthralgia (tab. 1). The most common physical finding was hepatomegaly (tab. 1), which corresponded to the etiological diagnosis. From the laboratory data, the notable findings were elevation of the inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen (tab. 2). The changes were not marked, and corresponded to the etiological causes of the illnesses. The patients with diagnosed diseases were treated with specific treatment with which at 6 month follow up they had recovered and the fever had resolved.

Table 2. Laboratory data in patients with vector-borne diseases (n=10) in a population with fever of unknown origin (FUO).

Variables	Normal range	Level in patients with vector-borne disease (mean±SD)
Albumin – blood	3.4–5.4 g/dL	38.67±4.4 g/dL
Aspartate transaminase	5–40 IU/L	30.2±29.6 IU/L
Alanine transaminase	5–40 IU/L	25.3±20.0 IU/L
Alkaline phosphatase	64–300 IU/L	230.88±101.4 IU/L
Creatine phosphokinase	<190 IU/L	43.6±10.5 IU/L
C-reactive protein	0.0–5.0 mg/L	35.2±35.0 mg/L
Erythrocyte sedimentation rate	≤20 mm/h	52.7±33.3 mm/h
Fibrinogen	2.0–4.5 g/L	6.0±1.7 g/L
Gamma-glutamyl transferase	10–50 IU/L	41.9±35.6 IU/L
Hemoglobin	130–180 g/L*	124.4±19.5 g/L
	120–160 g/L†	
White blood cells	3.5–10.5×10^9/L	7.0±2.5×10^9/L

* Male, † Female

DISCUSSION

This retrospective study is the first systematic evaluation of FUO in Bulgaria. It was conducted in a university hospital in the capital. One of the limitations of the study is that the patients were hospitalized and analyzed by an infectious diseases (ID) specialist, in the Department of Infectious Diseases, which may have produced a bias in the prevalence of infections as a cause of FUO. Another explanation for the high prevalence of infective causes of FUO is that Bulgaria is situated in South-East Europe at the edge of the Mediterranean region and has individual distinctions, such as climatic features and endemic areas of infectious diseases. Infections are the most frequent causes in cases of FUO in countries as India, Taiwan, Turkey and China (tab. 3). These countries are situated in South-East Asia and South-East Europe. Based on the local characteristics in Bulgaria a prevalence of infectious diseases is logical.

A study of the chronological order of the findings in the literature review for FUO suggests that the distribution of causes is changing. The leaders are infections and NIID, which are close to each other. Although infective conditions are still the leader in some countries (tab. 3), vector-borne infections consist a rare cause of FUO, according to other publications (tab. 3). These kinds of illnesses have a special clinical presentation and epidemiology, and in most cases

Table 3. Documentation of prevalence of vector-borne diseases (VBD) among patients with classic fever of unknown origin (FUO).

Author	Year of publication	Country	Patients (n)	Etiology (%)					VBD (%)
				ID	N	NIID	Mis	Un	
Petersdorf et al[1]	1961	USA	100	36.0	19.0	15.0	23.0	7.0	1.0
Barbado et al[12]	1992	Spain	218	22.9	22.0	19.3	17.0	18.8	1.8
Kazanjian[13]	1992	USA	86	32.6	24.4	20.9	12.8	9.3	1.2
Kejariwal et al[14]	2001	India	100	53.0	17.0	11.0	5.0	14.0	8.0
Liu et al[15]	2003	Taiwan	78	42.3	6.4	20.5	7.7	23.1	1.3
Tabak et al[16]	2003	Turkey	117	34.0	19.0	23.0	10.0	14.0	1.7
Vanderschueren et al[17]	2003	Belgium	290	19.7	10.0	23.5	13.1	33.8	1.0
Sipahi et al[18]	2007	Turkey	857	47.0	14.7	15.9	6.1	16.1	1.6
Hu et al[19]	2008	China	122	36.0	13.0	32.0	5.0	14.0	1.6
Moawad et al[20]	2010	Saudi Arabia	98	32.7	18.3	14.3	17.3	17.3	2.0
Mete et al[21]	2012	Turkey	100	26.0	14.0	38.0	2.0	20.0	1.0
Shi et al[22]	2013	China	997	48.0	7.9	16.9	7.1	20.1	0.5

ID: Infectious diseases, N: Neoplasia, NIID: Non-infectious inflammatory diseases, Mis: Miscellaneous, Un: Undiagnosed, VBD: Vector-borne diseases

they present as acute febrile syndromes.[23] In our study the proportion of vector-borne conditions was not small (31.3% of all infections). This high percentage may be related to the high number of diagnosed cases, and in particular the prevalence of infectious diseases. Other explanations are that Bulgaria is an endemic area for tick-bite diseases, and that there is a lack of a systemic protocol for evaluation of FUO in this country. Many patients had already lost time in various different consultations and investigations before their first examination by an ID specialist. The ID specialist is the medical consultant who can best analyze the case and compose the management of FUO.

In conclusion, the first Bulgarian retrospective FUO study identified infectious diseases as the most common causes of prolonged fever. Vector-borne diseases, and in particular tick-bite diseases, are not rare as a cause of FUO. The percentage of vector-borne infections as a cause of FUO in this study is higher than in other reports. This can be explained by the climatic, endemic and economic characteristics of the country. The absolute rate is not so high in the context of the whole population examined in the study. The clinical message is to refer cases of FUO to the ID specialist and to think about vector-transmitted illnesses in the differential diagnosis of FUO.

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ΠΕΡΙΛΗΨΗ

Συχνότητα νοσημάτων μέσω ενδιάμεσου ξενιστή σε ασθενείς με πυρετό άγνωστης αιτίας σε ένα βουλγαρικό νοσοκομείο

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ΣΚΟΠΟΣ Ο πυρετός άγνωστης αιτιολογίας (ΠΑΑ) είναι μια πολύπλοκη και προβληματική κατάσταση. Οι αιτίες του διακρίνονται σε 5 ομάδες: λοιμώξεις, νεοπλασίες, μη λοιμώδη φλεγμονώδη νοσήματα, διάφορα νοσήματα και αδιάγνωστες περιπτώσεις. Σκοπός της παρούσας μελέτης ήταν η εκτίμηση της συχνότητας και η περιγραφή των κλινικών και των εργαστηριακών ευρημάτων των ασθενών με νοσήματα μέσω ενδιάμεσου ξενιστή που εκδηλώνονταν με ΠΑΑ. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Αναδρομικά αναλύθηκαν 78 ασθενείς με εμπύρετο σύνδρομο για χρονικό διάστημα 4 ετών στο Τμήμα Λοιμωδών Νοσημάτων της Στρατιωτικής Ιατρικής Ακαδημίας της Σόφιας (Βουλγαρία). Ελήφθη πλήρες ιατρικό ιστορικό και πραγματοποιήθηκε κλινική εξέταση και εργαστηριακή διερεύνηση. Η τελική διάγνωση βασίστηκε στα κλινικά, στα επιδημιολογικά και στα εργαστηριακά δεδομένα. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Τα τροποποιημένα κριτήρια των Petersdorf-Beeson για ΠΑΑ πληρούσαν 54 ασθενείς. Η τελική διάγνωση τέθηκε σε 45 από αυτούς, ενώ λοιμώδες νόσημα βρέθηκε σε 32 (59,3%) ασθενείς. Νοσήματα μέσω ενδιάμεσου ξενιστή διαπιστώθηκαν σε 10 ασθενείς. Η διάγνωση καθορίστηκε σε 7 ασθενείς ως ρικετσίωση (*R. conorii* 2/10 και *C. burnetii* 5/10), μικτή λοίμωξη με *C. burnetii* και *C. pneumoniae* σε έναν ασθενή και νόσος του Lyme σε δύο ασθενείς. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η κύρια αιτία περιπτώσεων ΠΑΑ στον βουλγαρικό πληθυσμό είναι λοιμώδη νοσήματα, σε συμφωνία και με άλλες δημοσιευμένες μελέτες της νοτιοανατολικής Ευρώπης. Μεταξύ των λοιμώξεων, καταστάσεις οι οποίες προκαλούν νόσους που μεταφέρονται με αρθρόποδα δεν είναι σπάνιες, όπως παρατηρήθηκε στο 31,3% των λοιμώξεων της παρούσας μελέτης. Στις εξηγήσεις γι' αυτό περιλαμβάνονται η γεωγραφική θέση, το κλίμα και η οικονομική ανάπτυξη.

Λέξεις ευρετηρίου: Νοσήματα που προκαλούνται μέσω ενδιάμεσου ξενιστή, Πυρετός, Πυρετός άγνωστης αιτίας, Συχνότητα

References

1. PETERSDORF RG, BEESON PB. Fever of unexplained origin: Report on 100 cases. *Medicine (Baltimore)* 1961, 40:1–30
2. DURACK DT, STREET AC. Fever of unknown origin – reexamined and redefined. *Curr Clin Top Infect Dis* 1991, 11:35–51
3. BLEEKER-ROVERS CP, VAN DER MEER JWM. Fever of unknown origin. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J (eds) *Harrison's principles of internal medicine.* 19th ed. McGraw-Hill, New York, 2015:135–142
4. HERSCH EC, OH RC. Prolonged febrile illness and fever of unknown origin in adults. *Am Fam Physician* 2014, 90:91–96
5. BAYMAKOVA M, PLOCHEV K, DIKOV I, POPOV GT, MIHAYLOVA-GARNIZOVA R, KOVALEVA V ET AL. Fever of unknown origin in a Bulgarian hospital: Evaluation of 54 cases for a four year-period. *J Clin Anal Med* 2016, 7:70–75
6. WRIGHT WF, MACKOWIAK PA. Fever of unknown origin. In: Bennett JE, Dolin R, Blaser MJ (eds) *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* 8th ed. Elsevier Saunders, Philadelphia, 2015:721–731
7. BALINK H. ^{18}F-FDG PET/CT in fever and inflammation of unknown origin. PhD Thesis. University of Amsterdam, Netherlands, 2015
8. BAYMAKOVA M. Fever of unknown origin in adults (Bulgarian). *General Medicine* 2015, 17:61–68
9. HOROWITZ HW. Fever of unknown origin or fever of too many origins? *N Engl J Med* 2013, 368:197–199
10. EFSTATHIOU SP, PEFANIS AV, TSIAKOU AG, SKEVA II, TSIOULOS DI, ACHIMASTOS AD ET AL. Fever of unknown origin: Discrimination between infectious and non-infectious causes. *Eur J Intern Med* 2010, 21:137–143
11. WORLD HEALTH ORGANIZATION. Media centre: Vector-borne diseases. WHO, fact sheet no 387, 2014. Available at: http://www.who.int/mediacentre/ factsheets/fs387/en/
12. BARBADO FJ, VÁZQUEZ JJ, PEÑA JM, ARNALICH F, ORTIZ-VÁZQUEZ J. Pyrexia of unknown origin: Changing spectrum of diseases in two consecutive series. *Postgrad Med J* 1992, 68:884–887
13. KAZANJIAN PH. Fever of unknown origin: Review of 86 patients treated in community hospitals. *Clin Infect Dis* 1992, 15:968–973
14. KEJARIWAL D, SARKAR N, CHAKRABORTI SK, AGARWAL V, ROY S. Pyrexia of unknown origin: A prospective study of 100 cases. *J Postgrad Med* 2001, 47:104–107
15. LIU KS, SHENG WH, CHEN YC, CHANG SC, HSIEH WC. Fever of unknown origin: A retrospective study of 78 adult patients in Taiwan. *J Microbiol Immunol Infect* 2003, 36:243–247
16. TABAK F, MERT A, CELIK AD, OZARAS R, ALTIPARMAK MR, OZTURK R ET AL. Fever of unknown origin in Turkey. *Infection* 2003, 31:417–420
17. VANDERSCHUEREN S, KNOCKAERT D, ADRIAENSSENS T, DEMEY W, DURNEZ A, BLOCKMANS D ET AL. From prolonged febrile illness to fever of unknown origin: The challenge continues. *Arch Intern Med* 2003, 163:1033–1041
18. SIPAHI OR, SENOL S, ARSU G, PULLUKCU H, TASBAKAN M, YAMAZHAN T ET AL. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990–2006. *Med Sci Monit* 2007, 13:CR318–CR322
19. HU Y, LU H, ZHANG Y, JIANG W, YIN Y, PAN X ET AL. Fever of unknown origin: Revisit of 142 cases in a tertiary Chinese hospital. *Biosci Trends* 2008, 2:44–46
20. MOAWAD MA, BASSIL H, ELSHERIF M, IBRAHIM A, ELNAGGAR M, EDATHODU J ET AL. Fever of unknown origin: 98 cases from Saudi Arabia. *Ann Saudi Med* 2010, 30:289–294
21. METE B, VANLI E, YEMISEN M, BALKAN II, DAGTEKIN H, OZARAS R ET AL. The role of invasive and non-invasive procedures in diagnosing fever of unknown origin. *Int J Med Sci* 2012, 9:682–689
22. SHI XC, LIU XQ, ZHOU BT, ZHANG LF, MA XJ, DENG GH ET AL. Major causes of fever of unknown origin at Peking Union Medical College Hospital in the past 26 years. *Chin Med J (Engl)* 2013, 126:808–812
23. CHRISTOVA I. Studies on etiological diagnosis and prevalence of tick-borne diseases in Bulgaria (Bulgarian). DSc Thesis. National Center of Infectious and Parasitic Diseases, Sofia, 2012

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