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Fever of Unknown Origin in Elderly Patients

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SUMMARY
Introduction Causes of fever of unknown origin are different. It is considered that it can be caused with over 200 different clinical entities. Aetiological causes differ according to different categories of age. Febricity in the elderly is at most the result of autoimmune processes, malignancies, bacterial infections and vasculitis.
Objective The aim of this study was to determine the most common characteristics of fever, the most common laboratory, bacterial and viral tests and to analyze applied therapy in patients with unknown febrile state, and to affirm final diagnosis in elderly patients, as well as younger than 65 years old, and to define outcome of disease in both groups of patients.
Methods Research comprised 100 patients who had been treated at the Infectious Disease Clinic of the Clinical Centre of Vojvodina in Novi Sad, during a three-year period, and in whom fever of unknown origin had been diagnosed. Patients were divided into two homogenous groups of 50 people. The first one (S) consisted of patients older than 65 years, and the second, control group (K) was constituted of patients younger than the age of 65. All of them were chosen by random sample method.
Results Average results of standard laboratory parameters of infection were obtained, such as erythrocyte sedimentation rate (ESR), fibrinogen, CRP, and especially leukocyte, and those were significantly higher in the group of elderly patients. The cause had not been found in 10% of elderly patient group, and in the younger group, not even in the third of patients. Among known causative agents dominant were infections, usually of respiratory and urinary tract, in both tested groups. Even 28% of the elderly had sepsis, and 10% endocarditis. Malignant diseases were more frequent in group of the elderly patients, and immune i.e. systematic disorders were evenly noticed in both groups of patients.
Conclusion Despite advanced studies in medicine, and existence of modern diagnostic procedures, fever of unknown origin is still today differential diagnostic problem.
Keywords: fever of unknown origin; febricity; febrile state; temperature

INTRODUCTION

Fever of unknown origin has always been a challenge for practitioners, and still is. Most febrile cases are transient and there is no need for diagnosis or specific therapy. Smaller number of these cases is persistent and difficult for diagnostic examination [1, 2].

It is a commonly accepted definition that febricity in the elderly can be defined as temperature exceeding 37.2°C taken orally or of ear drum, or higher than 37.5°C taken rectally [3, 4, 5]. Considering that the elderly, due to slower metabolism or large number of drugs taken, have lower basal body temperature, every increase over 1.1°C compared to basal body temperature, is presumed as febrile response [6, 7].

According to some definitions (Petersdorf, Beeson) fever of unknown origin is a recurring phenomenon of higher body temperature above 38.3°C taken rectally, or above 37.8°C taken orally in the period of three weeks, whose source remains unknown after a week of hospital treatment, which included anamnesis, physical examination, as well as routine checkup, such as radiography lung scan, laboratory tests of blood and urine, as well as blood and urine examination for bacteria. The definition has survived for almost three decades. After that, it has been reviewed for several times [8, 9].

There are very different causes of typical cases of fever of unknown origin. It is considered that it can be caused by over 200 various clinical entities [10, 11, 12]. According to studies of Mexican researchers, the number of infectious causative agents was reduced with every ten years for the past four decades, but the number of autoimmune and neoplastic causative agents of unknown febricity increased [13].

Many researchers have dealt with comparison of febricity causes with the elderly in relation to younger adult population [14]. Results indicate that the relevant aetiological causes vary in these age categories. Febricity in the elderly is most commonly the result of autoimmune processes, malignancy, soft tissue infection, vasculitis, osteomyelitis; and diabetics are particularly prone to bacterial and fungus infections [15].

According to some research, in patients older than 65 years, infections show a decrease, and take second or even third place among the most common causative agents of unknown origin febricity. In developed countries, connective tissue diseases are the leading causative agents of febricity in the elderly increase concerning all infections. Although the most frequent syndromes are temporarily arthritis and rheumatic polymialgy, this diagnosis can easily be omitted or delayed, because their symptoms are subacute and nonspecific [16, 17].

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For the purpose of diagnosing unknown origin febricity, certain diagnostic procedures according to standard protocols are performed [18, 19].

In scientific literature the term 'potential diagnostic key' is mentioned, which represents some kind of a guideline for diagnostic procedures [20]. There also exist the procedures performed routinely, and those undertaken within the extended diagnostic, sometimes as the very last steps of procedure, and these are often very expensive and uncomfortable for the patient (invasive).

OBJECTIVE

The main aim of the study was to determine fever characteristics, the most common laboratory, bacterial and viral findings, and to analyze the applied therapy with patients with unknown origin febrile state. The goal was also to define the final diagnosis in patients the older, as well as younger than the age of 65; to determine outcome of disease in both groups of patients, and to establish the protocol, i.e. to suggest diagnostic and therapeutic algorithm for patients over 65 years old.

METHODS

Research was conducted in retrospective. It comprised 100 patients who were treated at the Infectious Disease Clinic of the Clinical Centre of Vojvodina in Novi Sad within a three year period, from January 2005 till December 2007, and who were referred to the Clinic, with the diagnosis of a febrile state of unknown origin. All of them satisfied the criteria according to definition of unknown origin febricity, in relation to temperature duration and previous tests.

Patients were divided into two equal groups of 50 patients. The first one (S) consisted of patients older than 65 years, and the second, control group (K), was constituted of patients younger than the age of 65. All of them were chosen by random sample method.

Standard laboratory, as well as all the other results, such as bacterial, viral, immunological and other additional test data were processed and analyzed. Afterwards, the applied therapy in both groups was analyzed, along with outcome of disease and final diagnosis. All the results provided by the research were further statistically processed using contemporary statistical methods and additionally analyzed and compared with researches done by other authors. Some recommendations have been proposed in accordance with the results obtained.

RESULTS

Elderly patient group (S) and control group (K) were uniform according to sex, i.e. percentage of male patients in the elderly group (56%) in relation to younger group (42%) pointed to no significant statistical difference (χ^2 test, p=0.1614).

Table 1. Body temperature levels the groups of patients

Temperature levels	Group	
	S	K
37.5-38.5°C	19 (38.0%)	14 (28.0%)
38.6-39.5°C	22 (44.0%)	28 (56.0%)
39.6-41°C	9 (18.0%)	8 (16.0%)

Measured temperature was analyzed in both groups of patients. Most of them had maximal daily temperature between 38.6 and 39.5°C (Tables 1). There was no statistically significant difference of body temperature levels, measured in these two groups of patients (χ^2 test, p=0.4638).

After the admission to hospital treatment, routine laboratory tests, especially those that indicate inflammation (the number of leucocytes) were done on all the patients, as well as C-reactive protein (CRP) which is the most sensitive reactant of inflammation in its acute phase. It was noticed that the average value of erythrocyte sedimentation rate, fibrinogen, CRP, and especially leukocyte was significantly higher in the group of elderly patients (Table 2).

The obtained data and mean values were compared between the groups in respect to the most frequent final diagnoses (infections, tumours and systemic diseases). The statistical analysis has shown, however, that there does not exist any statistically significant difference for any of the values between the patient groups.

Afterwards, bacterial analyses were done, first of all urine, blood, faeces, throat and nose culture, wound, cannula, urethra etc. It is needed to mention that all patients were taking antibiotics prior to sampling materials.

The most common isolated causative agent of urine was Escherichia coli in both groups, but in higher percentage in the group of elderly patients. Haemoculture was positive in only 2 (6%) patients of group K and even 19 patients (47.5%) of group S. The most common causative agents in this group were Staphylococcus sp. and in minor share Enterococcus sp. and Escherichia coli. There were no statistically significant differences between percentages of patients with negative urinoculture results and patients with isolated bacteria in these two groups (χ^2 test, p=0.074).

Rate of patients with isolated bacteria in haemoculuture in group S (48%) was statistically higher than in group K (6%), i.e. groups were not homogenous ad hoc (χ^2 test, p=0.0001).

Table 2. Values of some basic laboratory parameters depending on the cause of febricity

Parameter	Cause of febricity	Group	
		S	K
Leukocytes (average)	Infection	11.42	16.66
	Tumour	14.20	13.73
	Systemic disease	13.15	13.25
ESR (average)	Infection	79/105	100/112
	Tumour	104/122	79/97
	Systemic disease	116/134	104/124
Fibrinogen (average)	Infection	7.16	7.38
	Tumour	6.00	7.62
	Systemic disease	7.56	8.24
CRP (increased)	Infection	29/30 (96.67%)	24/24 (100%)
	Tumour	8/9 (88.89%)	3/3 (100%)
	Systemic disease	6/6 (100%)	5/6 (83.33%)

The cause of febricity was not found in patients on whom the mentioned diagnostic procedures were performed, so additional immune examinations were done, first of all antinuclear factors (ANF), antibodies of cumulative substrate, C3 and C4 complement, circulating immune complex (CIC) etc. Any statistically significant difference between tested groups regarding immune tests in groups S and K (p=1) was not found.

After routine laboratory tests were done, other additional analyses were performed, at first noninvasive and even invasive tests, later on. The most commonly used diagnostic procedures in both tested groups were radiography of the lungs and ultrasonography of the upper abdomen, according to diagnostic protocols, while other procedures were considerably rarely performed. Additional examination methods were more frequent in the group of elderly patients (S).

Eventually, final diagnoses in patients with febricity of unknown origin were analyzed. The cause was not found in 10% of elderly patient group, and in the younger group, not even in one third of the patients.

Among the diagnosed causative agents predominant were the infections, usually of respiratory and urinary tract, in both tested groups. Even 28% of the elderly had sepsis, and 10% endocarditis. Malignant diseases were more frequent in the group of the elderly patients, and immune i.e. systematic disorders were evenly noticed in both groups of patients (Table 3).

Statistically high significance was actually found in relation to unspecified aetiology of febricity among tested groups i.e. much larger number of patients in the group of younger (K) had temperature of unknown aetiology, while with the group of elderly patients (S) febricity cause was more often found (p=0.007).

Regarding infection as the cause of febrile state, statistically significant difference between groups S and K (p=0.358) was not found. Concerning urinary infection, between groups S and K, statistically significant difference was also not found (p=0.4098). Yet, statistically significant difference related to respiratory infections between groups S and K was noticed; respiratory infections were more frequent in the group of younger patients than the older ones (p=0.170). In relation to endocarditis, a statistically significant difference between tested groups (p=0.2453) was not found.

Regarding sepsis, statistically significant difference between groups S and K was noticed, much higher number of affected in older group of patients had sepsis, while in younger group no one had it (p=0.0001).

Statistically significant difference concerning tumours as final diagnosis was not found between the tested groups, either (p=0.1212).

Antibiotic therapy was in most cases applied parenterally, usually by combining two or more antibiotics (ex. cefriaxone and ciprofloxacin, or both in combination with metronidazole). There exist statistically significant difference in relation to application of antibiotics between the tested groups, as those were much more frequently used in elderly patient groups (p=0.0397). The antibacterial therapy in most of the patients was performed ex juvantibus, after taking the material for bacterial tests, and was corrected when necessary, after the antibiogram had been obtained.

Table 3. Final diagnosis of fever of unknown origin in groups of both ages

Final diagnosis	Group	
	S	K
Infection	30 (60.0%)	24 (48.0%)
Tumour	9 (18.0%)	3 (6.0%)
Systemic disease	6 (12.0%)	6 (12.0%)
Febris non specificata	5 (10.0%)	17 (34.0%)

Corticosteroid therapy (per os and parenterally) was applied in 8 older (16%), and 6 (12%) younger patients. The treatment was performed ex juvantibus in most patients, but always after an immunologist had been consulted and after excluding infective (lack of reaction to antibiotics and negative bacterial culture) and malignant aetiology of the fever (performing other diagnostic procedures). Regarding this kind of therapy, there was no statistically significant difference between groups S and K (p=0.7742).

Outcome of disease was much more favourable in younger patient group (K) that is 92%, while in group (S) it was 56%. In group (K) there was no fatal outcome, but in group (S) it was with as much as 6 (12%) of tested patients. The most common cause of death was sepsis, in 4 patients, malignant tumour in one patient and rupture of the so called mycotic (bacterial) aneurism of abdominal aorta, in one case. There is statistically significant difference concerning outcome of disease in these two groups of tested patients. Outcome of disease was a lot more favourable in the younger patient group (χ^2 test, p=0.0004).

DISCUSSION

According to many authors, the diagnostics of FUO in the elderly often differs from the one in young patients. The manifestation of a disease is often nonspecific in older patients. The physiologic reserves are diminished in the elderly, as well as their immunity. Many other, accompanying diseases, exist (comorbidity) that determine the further diagnostics and treatment, and hence the outcome of the illness. The symptoms and signs of many illnesses are atypical, or less prominent in older patients, which obviously complicates diagnostics. Thus for instance, cognitive function disorders can be the only sign of infection in the elderly [21, 22, 23].

Although it is known that the elderly possess diminished thermal response, compared with younger population, no statistically significant difference has been found in this study in respect to either the length of fever or maximal daily temperature between the two groups. This is probably due to the fact that the length of the fever and the temperature level (and not other symptoms and signs) had been prerequisite for the diagnoses of FUO and inclusion into the research.

The analysis of final diagnoses has shown that in case of FUO, it was not established in 10% of the elderly group,

and in 34 % of the patients from the control group. The difference is statistically significant (p=0.007). The cause of febricity was more often determined in the elderly. Other authors have come to similar conclusion; some studies show that undetermined cause of FUO can reach 30% [24, 25, 26]. One possible explanation might be that the decrease of temperature occurred faster in the young, more often leading to complete recovery without the final diagnoses. The other reason might be that the elderly exhibited prominent signs of some diseases sooner, while it sometimes took months to confirm a diagnosis clinically or by laboratory tests.

Among known causative agents, infections dominate in this investigation (60% in the elderly group, and 48% in the young), mostly of the urinary tract and the respiratory system. A statistically significant difference between the groups was not found in respect to FUO caused by infections (p=0.358). Other authors present similar results – 33.3% in the young and 45.5% in the elderly [27, 28]. This should not be a surprise, with febricity being still the most often manifestation of infections in both groups.

In the case of endocarditis no statistically significant difference between the groups was noted (p=0.2453), although 3 of the elderly patients and none of the young exhibited endocarditis. This might be contributed to the fact that the older patients more often had sepsis (and endocarditis). Also, the changes in cardiac valves and diminished vascularisation are more common in the elderly, which are also suitable for the onset of infection. The disease as the cause of FUO has been pointed out by other authors as well; hence one should consider it while planning diagnostic procedures and echocardiography should be included into the regular diagnostic of FUO in the elderly.

In respect to sepsis, statistically high difference was noted between the groups. The number of patients with sepsis was outstanding (28%), while none of the young had it as the cause of FUO (p=0.0001). Many causes lead to the penetration of bacteria into blood and to a thread of pathogenic events, and finally sepsis. Some of them are physiological weakening of barriers in the elderly, as well as multiorganic dysfunction, especially of vital organs.

Despite the fact that the malignant diseases were more common in the elderly FUO patients (18%) than in the young (6%), the difference was not significant (p=0.1212). Other studies also cite malignant diseases, especially of the digestive, respiratory and haematological systems, as the cause of febricity. Lately, an increase in the number of malignant diseases has been noted in the general population, due to the style of living and length of life, as well as to the presence of carcinogens in the environment. Taking this into the account and following the contemporary oncologic trends, the diagnostics of such diseases (tumour markers, colonoscopy), should be included into the FUO diagnostic procedures as early as possible.

The immunologic, i.e. systemic disorders were equally distributed between the groups. These results are congruent with other authors [29, 30]. The immune system, cellular as well as humoral, is weakened in the elderly, but younger persons react more vigorously to the autoimmune events. According to a study by Japanese authors, systemic disorders are the second most common cause of FUO, immediately after infections, in both the young and the elderly.

The outcome was more favourable for the control group (92%), than for the elderly (56%). While no fatal outcome occurred in the young, while it did in 12% of the elderly, with sepsis as the most common cause. The statistically significant difference has been found between the outcome in the two groups of patients (p=0.0004). This is a comprehensible result, as the older patients have diminished clinical response to infections, as well as malignant and systemic diseases. Multimorbidity, very frequent in this age, considerably contributes to the unfavourable outcome of many illnesses. According to one study that encompassed 97 FUO patients, 13.6% of the elderly and 14.7% of the younger ones died, which is different from what we have observed. According to some researches, the five-year death rate in the patients with undiagnosed FUO is around 3.2% [31, 32].

CONCLUSION

Despite the advanced studies in medicine, and the existence of modern diagnostic procedures, fever of unknown origin is still today a differential diagnostic problem. Our research has also confirmed that fact, as in both groups the cause of FUO has not been established in many cases. Considering different possible causative agents in elderly patients in relation to younger than 65 years old, it is needed to modify standard diagnostic algorythm, i.e. adapt them to elders so that attention can be turned earlier to tumours, systemic disorders (bear in mind temporal arteritis) and specific localisations of infections (e.g. endocarditis).

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Нејасна фебрилна стања код особа старије животне доби

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КРАТАК САДРЖАЈ
Увод Узроци повишене температуре непознатог порекла су различити. Сматра се да она може бити узрокована са више од двеста различитих клиничких ентитета. Етиолошки узрочници су различити у различитим старосним категоријама болесника. Фебрилност код особа старије животне доби најчешће је резултат аутоимунских процеса, малигнитета, бактеријских инфекција и ваксулитиса.
Циљ рада Циљ рада је био да се установе најчешће одлике стања повишене температуре, анализирају најчешћи лабораторијски, бактериолошки и вирусолошки налази и примењена терапија код болесника с нејасним фебрилним стањем, потом утврде коначне дијагнозе код испитаника старијих и млађих од 65 година и исход болести ових болесника.
Методе рада Истраживањем је обухваћено 100 болесника који су лечени на Клиници за инфективне болести Клиничког центра Војводине у Новом Саду током трогодишњег периода под дијагнозом нејасног фебрилног стања. Болесници су сврстани у две групе од по 50 испитаника, где су прву групу (С) чинили болесници старији од 65 година, а контролну групу (К) болесници млађи од 65 година.
Резултати Средње вредности основних лабораторијских параметара запаљења (седиментација еритроцита, фибриноген, *CRP*, леукоцити) биле су знатно веће код болесника старијих од 65 година. Код пет болесника (10%) прве и трећине испитаника друге групе није откривен разлог фебрилности. Међу познатим узрочницима овог стања утврђене су инфекције респираторног и уринарног тракта, и то у обе групе испитаника. Код чак 14 старих болесника (28%) дијагностикована је сепса, док је код петоро (10%) установљен ендокардитис. Малигне болести биле су чешће код испитаника прве групе, а имунолошка, односно системска обољења забележена су у обе групе подједнако.
Закључак Нејасна фебрилна стања и данас, упркос напретку медицине и савременим дијагностичким поступцима, остају диференцијалнодијагностички проблем.
Кључне речи: повишена температура непознатог порекла; фебрилност; фебрилно стање; температура

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