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Key diagnostic features of fever of unknown origin: Medical history and physical findings

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Abstract

Background: Fever of unknown origin (FUO) has many possible causes, so detailed history taking and physical examination are required. We identified key diagnostic features of medical history and physical findings for an efficient diagnosis of FUO.

Methods: A total of 42 consecutive patients (mean age: 50.6±20.3 years) with classic FUO were retrospectively recruited from January 2010 to March 2012. Key diagnostic features were identified from among diagnostic criteria for underlying diseases, indicators for diagnostic tests, and more useful factors for differential diagnosis.

Results: The mean number of abnormal findings per patient was 5.8 from taking the history and 2.0 from performing physical examination. In addition, the mean number of key diagnostic features identified was 0.7 (14.0%) from history taking and 0.6 (35.0%) from physical examination. The most relevant key diagnostic feature was arthritis, followed by cervical lymphadenopathy, dyspnea (with hypoxia), and ocular symptoms.

Conclusion: The usefulness of certain features of medical history and physical findings for diagnosing FUO was determined. Focusing on arthritis, cervical lymphadenopathy, dyspnea with hypoxia, and ocular symptoms might improve diagnostic efficiency in patients with FUO.

KEYWORDS

fever of unknown origin, key diagnostic features, medical history, physical finding

1 | INTRODUCTION

Fever of unknown origin (FUO) can be caused by many infections, non-infectious inflammatory diseases (NIID), malignancies, and other conditions. Thus, a detailed history taking and physical examination, laboratory tests, and imaging studies are required for diagnosis of FUO. Most previous investigations of FUO have focused on its etiology and prevalence,[1] outcomes, or the diagnostic value of investigations such as serum procalcitonin,[2,3] F-fluorodeoxyglucose positron emission tomography,[4,5] or invasive procedures. However, the clinical usefulness of medical history and physical findings has not been investigated thoroughly.[6] Therefore, we performed this study to identify the key diagnostic features of FUO with respect to medical history and physical findings.

2 | METHODS

This retrospective study assessed consecutive patients with FUO attending the outpatient clinic of the Department of General Internal Medicine at Hiroshima University Hospital from January 2010 to March 2012. Classical FUO was diagnosed according to the following criteria of Naito et al.[1]: (i) fever with a temperature >38°C at least twice during a ≥3-week period, (ii) unknown etiology of fever after

three outpatient visits or 3 days of hospitalization, and (iii) no HIV infection or immunodeficiency before the onset of fever.

We collected abnormal medical history and physical findings from the medical records, and assessed their usefulness. Useful features were identified from among diagnostic criteria for underlying diseases, indicators for the selection of diagnostic tests, and factors that assisted in making a differential diagnosis. For example, lymphadenopathy was defined as a useful feature in patients diagnosed with adult Still's disease, because it is one of the diagnostic criteria for this disease.[7] The useful rate of medical history and physical findings was the number of useful features divided by the total number, respectively. The key diagnostic features were determined from higher useful rate. This study was approved by Hiroshima University Hospital ethics committee, which waived the need for informed consent because of its retrospective observational design. The study was conducted in accordance with the principles of the Helsinki Declaration of 1975, as revised in 2000.

3 | RESULTS

A total of 42 patients with FUO were enrolled, including 24 men and 18 women aged from 19 to 86 years (mean±standard deviation: 50.6±20.3 years). The underlying cause of FUO was infection in seven patients (16.7%), NIID in 18 patients (42.9%), malignancy in five patients (11.9%), other diseases in three patients (7.1%), and unknown in nine patients (21.4%) (Table 1).

A mean of 5.0 abnormal medical history per patient were obtained, among which the mean numbers of key features was 0.7 (14%). There was a mean of 1.7 abnormal physical findings per patient, among which the mean number of key features was 0.6 (35.0%) (Tables 2 and 3). The most relevant key diagnostic feature was arthritis, followed by lymphadenopathy, dyspnea, and ocular symptoms (Table 4). Among eight patients with arthritis, seven were diagnosed as having NIID. On the other hand, there were 20 patients with joint pain; nine were diagnosed as NIID; and two were diagnosed with viral infection. Arthritis was not observed in the patients with viral infection. The duration of joint pain differed between patients with NIID and patients with infection (6.4 weeks vs 1.8 weeks). Among eight patients with cervical lymphadenopathy, malignant lymphoma was diagnosed in three and one had adult-onset Still's disease. Cervical lymphadenopathy as a key feature was defined as lymph nodes larger than 1.0 cm (major axis) in size persisting for at least 2 weeks. In all patients with dyspnea, hypoxia ($SPO_2 \leqq 95\%$) was present and significant abnormal findings were obtained by computed tomography (CT). Among four patients with dyspnea (with hypoxia), miliary tuberculosis and interstitial pneumonia were diagnosed in one patient each. Of five patients with ocular symptoms (such as congestion, blurred vision, double vision, dry eyes, or eye pain), one had scleritis of Takayasu disease and one had uveitis secondary to sarcoidosis.

TABLE 1 Causative diseases of FUO

NIID 18 (43%)	Takayasu arteritis×2, ANCA-associated vasculitis×2, RA×2, JRA, ASD×2, PMR×2, Castleman's disease×2, SLE, sarcoidosis, interstitial pneumonia, FMF, human adjuvant disease
Infection 7 (17%)	Miliary tuberculosis, pneumonia, liver abscess, wound infection, viral meningitis, acute HIV infection, CMV hepatitis
Malignancy 5 (12%)	Malignant lymphoma×4, paraneoplastic syndrome (rectal cancer)
Others 3 (7%)	Drug fever, pregnancy, psychogenic fever
Unknown 9 (21%)	

NIID, non-infectious inflammatory disease; ANCA, antineutrophil cytoplasmic antibody; RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; ASD, adult Still's disease; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; FMF, familial Mediterranean fever; HIV, human immunodeficiency virus; CMV, cytomegalovirus.

TABLE 2 Abnormal features obtained from medical history and physical findings

Abnormal features
Medical history
Joint pain, 20; rash, 17; anorexia, 17; malaise, 15; cough, 14; weight loss, 12; anamnesis, 12; chill, 10; headache, 10; stomach ache, 9; edema, 9; diarrhea, 7; back pain, 7; sputum, 6; eye symptom, 5; sore throat, 5; lymphadenopathy, 5; chest pain, 5; dyspnea, 4; history of exposure, 4; insomnia, 3; night sweats, 3; numbness, 3; stomatitis, 2; hair loss, 2; sunlight hypersensitivity, 2; travel history, 1
Physical findings
Rash, 9; relative bradycardia, 8; arthritis, 8; lymphadenopathy, 8; edema, 7; abnormal breath sounds, 7; costovertebral angle tenderness, 4; pallor of conjunctiva, 2; tonsillar enlargement, 2; impaired consciousness, 1; dementia, 1; jolt accentuation positivity, 1; alopecia, 1; uveitis, 1; scleritis, 1; dental caries, 1; thyromegaly, 1; abnormal heart sounds, 1; obesity, 1; scrotal swelling, 1; numbness, 1; wound infection, 1; tachycardia, 1

TABLE 3 Useful rate of medical history and physical findings

	Abnormal features per cases	Useful features per cases	Useful rate (%)
Medical history	5.0	0.7	14.0
Physical findings	1.6	0.6	35.0

4 | DISCUSSION

In the present study, the usefulness of the history and physical findings for diagnosing of FUO was investigated. This is the first report on key diagnostic features of FUO in Japan, and we found that arthritis, lymphadenopathy, dyspnea, and ocular symptoms were the main key features.

The most useful key diagnostic feature of FUO was arthritis, which was a particular clue to the diagnosis of NIID. If there is a history of

TABLE 4 Key diagnostic features and final diagnosis of useful cases

Key diagnostic features	Useful/total (%)	Final diagnosis of useful cases
Arthritis	7/8 (86)	ASD, RA×3, PMR, sarcoidosis, human adjuvant disease
Lymphadenopathy	4/8 (50)	Malignant lymphoma×3, ASD
Dyspnea	2/4 (50)	Miliary tuberculosis, interstitial pneumonia
Eye symptom	2/5 (40)	Takayasu arteritis, sarcoidosis
Medical history	6/17 (35)	Postoperative wound abscess, liver abscess, drug fever, HIV infection, human adjuvant disease, pregnancy
Rash	4/17 (23)	HIV infection, ASD, RA, human adjuvant disease, pregnancy
Cough	3/14 (21)	Miliary tuberculosis, GPA, atypical pneumonia

ASD, adult Still's disease; HIV, human immunodeficiency virus; CMV, cytomegalovirus; GPA, granulomatosis with polyangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PMR, polymyalgia rheumatica; FMF, familial Mediterranean fever.

joint pain for longer than 6 weeks, the patient should be actively assessed for arthritis. If arthritis is found, it is important to investigate NIID. The second useful key feature was lymphadenopathy, especially cervical lymphadenopathy. Other studies performed overseas have demonstrated that an increased likelihood of malignancy, including malignant lymphoma, acute or chronic leukemia, and metastatic lymphadenopathy, is associated with lymph nodes more than 2 cm in size (nodes <1 cm are almost always benign), persistence for >2 weeks, and supraclavicular or generalized distribution (at least two sites).[8-11] All of the patients diagnosed with malignant lymphoma in our study had enlarged cervical lymph nodes, and three or more enlarged nodes were detected by CT. Therefore, we consider evaluation by CT desirable in FUO patients with cervical lymphadenopathy to diagnose malignant lymphoma. In all patients with dyspnea as a key feature, hypoxia was present and significant abnormal findings were obtained by CT. Pulse oximetry is an objective and simple examination for evaluating hypoxia. If a low SPO_2 is detected, the patient should be considered to evaluate by CT.

Ocular symptoms provided useful clues in two patients, one of whom had uveitis, while a diagnosis of scleritis was made in the other. There are reports about the frequency of systemic diseases associated with these ocular conditions, so it was easy to narrow the differential diagnosis. The most frequent systemic disease was NIID. According to an epidemiological study of uveitis in Japan, frequent causative diseases were sarcoidosis, Vogt-Koyanagi-Harada disease, and Behcet's disease.[12] In addition, the systemic diseases often accompanied by scleritis were rheumatoid arthritis, vasculitis syndrome, inflammatory bowel disease, and systemic lupus erythematosus.[13] While the most frequent disease is rheumatoid arthritis, vasculitis syndrome cannot be ignored in the differential diagnosis of scleritis despite the difference in prevalence. Symptoms of uveitis are blurred vision, floaters, photophobia, loss of vision, eye pain, and redness. The characteristic symptoms of scleritis are hyperemia and severe eye pain, while it can also cause loss of vision and eye movement disorders. If we encounter such symptoms in FUO patients, it is necessary to arrange an ophthalmology consultation.

The present study had the following limitations. (i) The number of subjects was small, so generalization of our conclusions is difficult. (ii) There was a possible that some of abnormal findings were missed because these were not recorded.

5 | CONCLUSION

In the present study, we evaluated key diagnostic features of the medical history and physical findings in patients with FUO, revealing the usefulness of certain features. The most relevant key feature was arthritis, followed by cervical lymphadenopathy, dyspnea with hypoxia, and ocular symptoms. Focusing on assessment of these abnormal features might improve the efficiency of investigating patients with FUO. In the future, the key features of FUO revealed in this study should be confirmed by multicenter prospective studies to improve the management of FUO.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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