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Low-grade fever: how to distinguish organic from non-organic forms

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SUMMARY

Background and aim: Low-grade fever (LGF) is defined as a body temperature between 37.5 and 38.3 °C, which is below the classical value reported for fever of unknown origin (FUO). We attempted to characterise its epidemiology, aetiology and clinical aspects to improve the methodological approach to diagnosis. **Design and Methods:** We reviewed and evaluated a survey of patients with LGF, followed as outpatients of our Department, a tertiary referral centre from 1997 to 2008. The same classifications were applied for classical FUO, and in the patients diagnosed with LGF, we also investigated for habitual hyperthermia (HH). **Results:** Seventy-three patients were selected and divided into two groups: group A included 32 patients classified with organic fever and group B included 41 patients with HH. Aetiology of organic LGF was: infectious disease 59%; neoplasm 3.1%; inflammatory non-infectious disease 6.2%; miscellaneous 18.7%; undiagnosed 12.5%. Mean age was significantly higher in the organic fever than in the HH group ($p < 0.02$). Splenomegaly and loss of weight were significantly associated with organic fever ($p < 0.05$), while dizziness and general malaise were associated with HH. Lack of any pathological signs at physical examination was significantly more frequent in HH ($p < 0.0001$). Among the biochemical tests, white blood cells and C-reactive protein were more frequently above normal limits in group A than in group B ($p < 0.05$). **Conclusions:** In our experience, LGF requires the same methodological diagnostic approach as FUO, because there is no relationship between body temperature values and the severity of the underlying diseases, and the aetiological spectrum is also the same.

What's known

In the literature reviews focused on low grade fever do not exist. There are only case report or cohort studies which indicate exceptional cases that do not reflect the overall epidemiological picture. Moreover, from these studies, it is not always possible to establish what the authors mean with low grade fever, nor the method used to measure it, nor the duration of the low grade fever, and the papers analysed deal only with organic low grade fevers and not with habitual hyperthermia.

What's new

This is the only study which tries to better define the habitual hyperthermia putting it in the sphere of low grade fevers rather than in the fever in general. To facilitate this study, we propose a flow-chart of simple execution, easy feasibility and excellent performance. On the contrary, we state that organic low grade fevers always have to be studied as FUO.

Introduction

Fever is one of the most common clinical manifestations referred by patients to their physicians (1). The challenge is to distinguish between fevers caused by the more or less serious pathologies, requiring a specific therapy, and those caused by the vast majority of other ailments, which instead often present a self-limited pathology. Fever is defined as an increase in body temperature mediated by a functional alteration of the regulatory centre of the hypothalamus, causing a rise in temperature towards the upper values of the set-point, the activation of the peripheral mechanisms of thermogenesis and the inhibition of those of thermodispersion (2,3). Hyperthermia, on the contrary, is an increase in body temperature independent of the physiological homeostatic control mechanisms, which do not, however, raise the hypothalamus set-point. In other words, it arises from a 'peripheral' alteration of the mechanisms of thermoproduction and thermodispersion.

Another important condition is the fever of unknown origin (FUO), which poses considerable problems for physicians, because although most diseases underlying FUO are treatable, they can be difficult to diagnose in a particular patient and for reasons which are not always clear (4–11).

Low-grade fever (LGF) commonly refers to a condition with a body temperature continually or intermittently between 37.5 and 38.3 °C. As in the case of fever, it is absolutely a symptom accompanying very many infectious, and autoimmune and neoplastic diseases. Sometimes, however, there is no particular organic pathology, as in the case of habitual hyperthermia (HH), which, rather than a disease, should

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be considered a paraphysiological variant of normal body temperature (6).

Habitual hyperthermia is a clinical condition characterised by a body temperature never higher than 38.3 °C, with an erratic circadian rhythm. It may persist for years and for rather complex reasons, and the normal body temperature of an otherwise perfectly healthy subject remains elevated. It is typical of young asthenic women prone to headaches and with vasomotor liability. Its diagnosis today is still possible, but only after an adequately prolonged period of observation and measurement of body temperature (6). Although FUO is widely recognised and is frequently reported, in our opinion, LGF has not received adequate attention in the literature. This work, therefore, reviews our clinical experience of patients with LGF, with the aim of shedding further light on its frequency, causes, management, work-up, prognosis and possible links with the much better-known forms of FUO.

Patients and methods

Our study group included all the cases referred for LGF between 1997 and 2008 as outpatients at our Department of Clinical Medicine, Policlinico Hospital, which is a tertiary referral centre.

Inclusion criteria were patients with axillary body temperature continually or intermittently between 37.5 and 38.3 °C for at least 3 weeks. Patients with axillary body temperature ≥ 38.3 °C at any time were considered to be classical FUO and, therefore, excluded. Patients who presented with LGF with particular symptoms or alarm signs (such as dysphagia, rectorrhagia, severe weight loss, neurological disorders, etc.), suggesting a serious organic disease were also excluded.

We used the same classification that is generally adopted for FUO, distinguishing between the classical diseases (infectious disease, neoplasm, inflammatory non-infectious disease) and diseases that are not easily classifiable (miscellaneous). In patients diagnosed with LGF, we also investigated for HH, a paraphysiological condition not associated with any organic disease (6).

The first diagnostic step was a detailed anamnestic investigation and thorough physical examination. The patients' axillary temperatures were then measured and they were asked to measure it in the same manner four times a day and to record results for 5 days in a special booklet. When the anamnestic and physical examination data indicated a strong hypothesis of organic LGF, further appropriate biochemical and instrumental tests were performed. If history was not indicative and/or physical examination was negative, a strong hypothesis of HH was made. In this case, only total blood cell count, erythrocyte sedimentation rate, C-reactive protein (CRP) and urine analysis were performed. If these were positive, clinical investigations continued with other examinations, otherwise a bi-monthly follow up for 2 years in the same manner and a continual monitoring of temperature were scheduled.

Statistical analysis was performed using Student's *t*-test, the chi-square test and the Fisher exact test, wherever appropriate. The diagnostic reliability of organic LGF was evaluated by calculating sensitivity, specificity, positive predictive value and negative predictive value, using standard formulas. $p < 0.05$ was considered significant.

Results

Eighty-two patients were selected and, on the basis of the final diagnosis, divided into two groups: group A included 32 patients (14 men, 18 women) with organic LGF, and group B included 50 subjects with HH. In the latter group, however, five subjects were excluded because they did not complete the planned follow up, and after telephone invitations to attend proved unsuccessful, they were considered to have dropped out. Forty-five patients (16 men, 29 women) were therefore eventually included in this group.

Aetiology of organic LGF (group A) is shown in Table 1. In 19 out of 32 patients (59%), it was because of underlying infectious disease; one patient (3.1%) had neoplasm, two (6.2%) had inflammatory non-infectious disease and six (18.7%) had miscellaneous causes. In four patients (12.5%), there was no definite diagnosis for organic LGF (undiagnosed LGF): biochemical tests showed only aspecific changes, imaging procedures were not diagnostic, and in any case the fever disappeared within 4 months.

Diagnosis of HH was hypothesised after the first evaluation, including history and physical examination, in 45/77 patients (58.5%). In four patients, however, the initial diagnosis was not confirmed and in the following 6 months these diagnoses were made: one intestinal bacterial contamination in a patient with dietary intolerance; one dental granuloma and one appendicitis with histological features of Crohn's disease; in the fourth case, sinusitis in a subject allergic to pollen with rhinitis was diagnosed after 12 months. A definitive diagnosis of HH was therefore made in 41 out of 77 patients after 2 years of follow up.

Mean age was significantly higher in the organic LGF group A than in the HH group B (34 ± 14 vs.

Table 1 Final diagnosis of patients with low-grade fever (LGF), diagnostic tools and hypothesised diagnosis at first evaluation

Diagnosis	Patients *n* (%)	Diagnostic tools	First evaluation
Mononucleosis	4 (12.5)	Serology	Organic LGF
Brucellosis	6 (18.8)	Serology	Organic LGF
Autoimmune thyroiditis	2 (6.3)	Autoantibodies/ultrasound scan	Organic LGF
Toxoplasmosis	2 (6.3)	Serology	Organic LGF
Cat-scratch disease	1 (3.1)	Serology	Organic LGF
Sinusitis	1 (3.1)	Radiography	Habitual hypertermia
Pulmonary actinomycosis	1 (3.1)	Histology	Organic LGF
Bacterial endocarditis	2 (6.2)	Transesophageal echocardiography	Organic LGF
Undiagnosed LGF	4 (12.5)	*	Organic LGF
Systemic lupus erythematosus	1 (3.2)	Autoantibodies	Organic LGF
Crohn's disease	2 (6.2)	Histology	Organic LGF
Ehlers-Danlos syndrome with diverticulitis	1 (3.1)	Colonoscopy	Organic LGF
Rheumatoid arthritis	1 (3.1)	Signs and symptoms/rheumatoid factor	Organic LGF
Food intolerance with bacterial overgrowth	1 (3.1)	Breath test	Habitual hypertermia
Dental granuloma	1 (3.1)	Orthopantomography	Habitual hypertermia
Appendicitis	1 (3.1)	Surgery	Habitual hypertermia
NH lymphoma	1 (3.1)	Histology	Organic LGF

*Serological and instrumental tests negative.

27 ± 9.2 years, $p < 0.02$). Within group B, age was significantly higher in men than women (31 ± 8.5 vs. 24 ± 5.5 years, $p < 0.05$); this difference was also present in group A, but it was not significant (36.7 ± 14 vs. 31.7 ± 14 years; p = ns).

Table 2 shows the symptoms referred by the two groups. Dizziness and a not well-defined general malaise were the symptoms significantly associated in group B. Loss of weight, on the contrary, was significantly associated to organic LGF (group A) ($p < 0.05$).

Table 3 shows the anomalies found at physical examination. Lack of any pathological signs at physical examination was more frequent in subjects with HH ($p < 0.0001$), while the rate of splenomegaly and weight loss were significantly greater in group A ($p < 0.03$ and $p < 0.05$ respectively).

Among the biochemical tests, white blood cells and CRP showed a higher number of elevated values in group A than in group B [10/32 vs. 1/41 ($p < 0.05$) and 9/32 vs. 1/41 ($p < 0.05$) respectively]. No difference was found between the two

Table 2 Referred symptoms of patients with organic LGF (group A) and habitual hyperthermia (group B)

Symptoms	Group A *n* = 32	Group B *n* = 41	p
Nausea	1	5	ns
Anorexia	1	5	ns
Arthralgia	8	4	ns
Headache	5	2	ns
Cough	3	2	ns
Chills	3	0	ns
Asthenia	3	6	ns
Abdominal pain	5	4	ns
Sore throat	4	3	ns
Sweating	3	0	ns
Dizziness	0	7	0.02
Pruritus	0	2	ns
Intercostal pain	0	2	ns
Not defined general malaise	0	15	0.0001
Weight loss	9	1	0.05

Table 3 Presence of signs at physical examination in the two groups of patients

Signs	Group A *n* = 32	Group B *n* = 41	p
No signs	2	30	0.0001
Lymphadenopathy	14	9	ns
Hepatomegaly	3	4	ns
Splenomegaly	6	0	0.03
Pharyngeal inflammation	3	0	ns
Skin lesions	1	0	ns
Cardiac murmur	3	0	ns
Pain on abdomen palpation	8	4	ns

Group A: organic LGF and group B: habitual hyperthermia.

groups for erythrocyte sedimentation rate (ESR) and urine analysis. None of the 41 subjects with a final diagnosis of HH, however, showed particular alterations in biochemical parameters in the follow-up period; therefore, the alterations found in two patients at commencement of the study could have been because of seasonal viruses.

Thirty-two of the 41 subjects with HH who completed the 24 months of follow up had stopped measuring their body temperatures and defined their general health condition as good. At the first step, our diagnostic evaluation incorrectly classified four subjects as HH (false positive), thus having 91% sensitivity and 87% specificity. After 6 months, diagnosis of HH was hypothesised in 42 patients, with only one patient still incorrectly labelled as HH, therefore with 97% sensitivity and specificity and 97% post-test probability of HH (Table 4). Consequently, on the basis of these results, we propose a diagnostic algorithm (Figure 1), which is easy to apply and is also highly efficient for outpatients, but obviously needs to be confirmed by further studies.

Table 4 Discrimination of habitual hyperthermia from organic low-grade fever (LGF) at first evaluation (panel A) and after 6 months of follow up (panel B)

	Habitual hyperthermia	Organic LGF
Panel A		
Correct diagnosis	41	28
Incorrect diagnosis	4	0
Panel B		
Correct diagnosis	41	31
Incorrect diagnosis	1	0

Sensitivity 97%; specificity 97%; positive post-test probability 97%, sensitivity 91%; specificity 88%.

Discussion

Fever of unknown origin is a well-defined entity with three classical diagnostic criteria, as first established by Petersdorf and Beeson: (i) illness of more than 3 weeks' duration, (ii) with a temperature higher than 38.3 °C on several occasions and (iii) no established diagnosis after 1 week of evaluation (4). Thirty years later, Durack and Street proposed a reduction in the third criterion from 1 week to 3 days of appropriate investigations, because of the progress in diagnostic techniques (12). The other two criteria have remained unchanged. However, the second criterion (fever > 38.3 °C) excludes a series of fevers below 38.3 °C, which must nevertheless be recognised to avoid discomfort to patients and prevent waste of public money, as they present a clinical course and pose diagnostic difficulties similar to those of FUO. In this report, we refer our experience of patients suffering from fever below 38.3 °C and propose an algorithm to facilitate a correct diagnosis.

Our results, in contrast with the few epidemiological data in the literature (4,5,12), show that the prevalence of HH is higher (54%) than LGF from

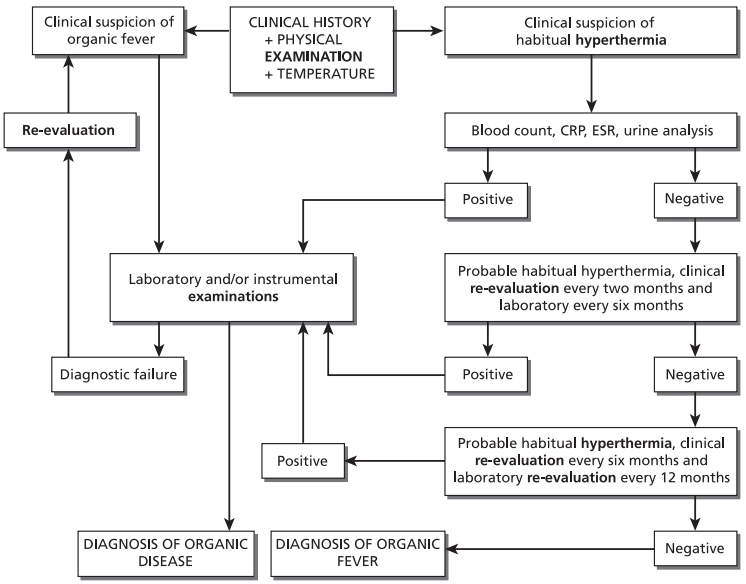

Figure 1 Algorithm for the diagnostic definition of low-grade fever

organic causes (46%). In the work of Knockaert et al. the prevalence of HH among FUO was as low as 2.5% (13). There may be various reasons for this difference:

- It could be because of a selection bias. Ours is a tertiary referral centre for fever pathologies and we are probably asked to investigate fevers for which no solution has been found in spite of the patient being followed for a long time by general practitioners or in non-specialised centres. HH may therefore be more difficult to evaluate than organic LGF;
- In the literature, HH is not always correctly defined and it is often mistakenly included with FUO, which, by definition, refers to patients with a body temperature ≥ 38.3 °C, while HH ≥ 38.3 °C is an exceptional event. In this category of patients, HH may thus have only a marginal epidemiological role.

In our study, the HH subjects were prevalently woman, although this result was not statistically significant. Little is known about the causes of this higher frequency, already reported in the literature (6). Clinical history in HH, in contrast with organic LGF, shows little of note: there is a prevalent symptomatology of cenesthopathy, dizziness and a not well-defined state of general malaise, which may also be correlated to a state of anxiety or depression as a consequence of the hyperthermia of unclear origin, as reported by Reimann (14). In contrast, weight loss is significantly associated with the organic forms. In this respect, it should be remembered that the above psychological states sometimes associated with HH should be investigated and evaluated because they could also lead to weight loss. In these cases, it may be useful to investigate for signs of weight loss and malnutrition during physical examination and in the laboratory tests.

Physical examination in our study population was negative in 73% of the HH patients compared with 6.2% in organic LGF, and the few clinical signs present in HH (for example lymphadenopathy and hepatomegaly), may be aspecific and misleading. Finally, simple and easily performable laboratory assays, such as total blood cell count and CRP were altered, with a higher frequency in organic LGF.

It should also be underlined that, as happens in FUO, a certain percentage of forms remain undiagnosed in LGF, in our study population 12.5%. These forms can be distinguished by the initial presence of laboratory alterations, which however, rapidly normalise with the disappearance of the LGF. Precisely, this difference in temperature evolution – a normalisation in organic LGF with unknown aetiology compared with a persistent fever in HH – suggests that HH in LGF may be simply interpreted as an adjustment of the hypothalamus set-point towards higher values, and therefore considered a paraphysiological variant rather than a pathological condition. It may simply be one of the two extremities of the Gaussian distribution of human body temperature: the higher one.

In the light of the data we obtained, it is important to underline two aspects:

- a prolonged follow up, as mentioned above, represents the only valid diagnostic tool to exclude organic pathologies in patients with LGF;
- the diagnostic approach of our study, from which we deduced the above-mentioned algorithm, presents a 97% probability of diagnosis of HH at 6 months. This would allow us to already reassure the patient during the first few visits. Only by doing so can we prevent the hypochondriac delirium, which leads a patient to become thermometer-dependent and to construct a host of more or less complex symptoms, building up a clinical picture, which at that point is difficult to diagnose and at times can only really be cured by a psychiatrist.

As regards organic LGF, the small number of cases in our population did not allow us to reach any definitive conclusions, and as mentioned above it is difficult to compare our results because of the very few reports in the literature. What emerges is that, as in the majority of cases of FUO, the most frequent cause was infection followed by miscellaneous causes. This would confirm the emerging role of inflammatory non-infectious disease, which is being more frequently reported in the various study populations (15–17). The very small number of neoplasm cases found is, on the contrary, at first sight, difficult to understand; this is probably as a result of the fact that these patients also presented with a serious and complex clinical picture with, apart from the LGF, alarm signals, which warranted hospitalisation rather than outpatient treatment.

In conclusion, the results of our study population suggest: (i) that HH in LGF patients is an important nosographical entity with a high prevalence, confirming the importance of diagnosing it by limiting the diagnostic approach to a thorough physical examination and few but specific laboratory tests, and (ii) that it is incorrect to make a clear and substantial difference between the management of LGF and FUO. In LGF, after the HH forms have been eliminated, diagnostic work-up should not be different to that of FUO because, in general, the causes of FUO can also be responsible for LGF.

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