Case Report

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Functional hyperthermia caused by obstructive sleep apnea syndrome: A case report

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Abstract

A 47-year-old farm worker with diabetes mellitus, dyslipidemia, and hyperuricemia was referred to our hospital for a 3-month history of fever and malaise. He had no respiratory tract or abdominal symptoms, skin rashes, or joint pain. There was no change to his regular medication or pesticide exposure. Blood tests and echocardiography revealed no abnormalities. Whole-body computed tomography revealed a fatty liver; however, non-alcoholic steatohepatitis was excluded. We diagnosed the patient with functional hyperthermia. He had a history of snoring and weight gain, and we suspected the obstructive sleep apnea syndrome to be a stressor. Polysomnography revealed severe obstructive sleep apnea syndrome with an apnea–hypopnea index of 44.5. Continuous positive airway pressure was introduced; the axillary temperature decreased gradually and malaise was resolved. Functional hyperthermia should be considered a cause of fever with a negative inflammatory response. Obstructive sleep apnea syndrome can be a stressor for functional hyperthermia, which can be improved by interventions.

Keywords

Continuous positive airway pressure, fever of unknown origin, functional hyperthermia, high body temperature, obstructive sleep apnea syndrome, psychogenic fever, stressor

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Introduction

Fever should be distinguished from hyperthermia when considering the causes of an elevated body temperature.[1] Hyperthermia is a thermoregulatory mechanism disorder characterized by excessive heat production and inadequate heat release without changes in the prostaglandin-mediated set-point of the thermoregulatory center.[1,2]

Functional hyperthermia is a typical condition that causes high body temperature without inflammation, and diagnosis requires the exclusion of other diseases with elevated body temperature, especially those with chronic inflammation.[1] Functional hyperthermia was previously known as psychogenic fever; however, in recent years, it has increasingly been referred to as functional hyperthermia because its mechanism differs from that of fever, and the stressors for the temperature rise are not exclusively psychogenic.[3] Since patients with the condition have no abnormal laboratory findings, physicians sometimes advise them to avoid worrying about the same; this does not always resolve the patients' concern.[4] Medical providers must diagnose and treat functional hyperthermia according to the patients' symptoms and condition.

The treatment of functional hyperthermia generally involves approaching the stressors, such as comorbid diseases and conditions. Obstructive sleep apnea syndrome (OSAS) presents with symptoms such as excessive daytime sleepiness and headache; however, there are no reports of OSAS causing an increased body temperature. To our knowledge, there are

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no English-language reports on the improvement of functional hyperthermia after treatment for OSAS.

Herein, we present the case of a patient with functional hyperthermia that improved following treatment of severe OSAS.

Case

A 47-year-old man with diabetes mellitus, dyslipidemia, and hyperuricemia was referred to our hospital with fever and malaise. He began complaining of fever in the 37.0°C–37.9°C range and malaise 3 months ago, leading to an increased absence from work. Diabetes mellitus was exacerbated due to decreased physical activity. No upper or lower respiratory tract symptoms, abdominal symptoms, skin rashes, and joint pain were noted. His regular medications (febuxostat, fenofibrate, lansoprazole, linagliptin, metformin, miglitol, olmesartan, and repaglinide) had not been changed, and he had no history of illegal drug use. He worked on a farm, but was not exposed to pesticides. Blood tests, including an interferon-γ release assay performed by the previous physician, revealed no abnormalities. Transthoracic echocardiography revealed no signs of infective endocarditis. Non-contrast whole-computed tomography revealed no obvious abnormalities other than a fatty liver. The cause of the fever was unclear, and the patient was referred to our hospital. At the time of his first visit to our hospital, no obvious abnormalities were observed in the vital signs (blood pressure, 137/93 mmHg; pulse rate, 73/min; and axillary body temperature, 37.3°C). Physical examination revealed no pharyngeal or tonsillar abnormalities, heart murmurs, abnormal sweating, necrosis of the skin, or lymphadenopathy. Blood tests revealed no inflammatory findings or abnormalities that could cause a fever (Table 1). A hepatologist ruled out non-alcoholic steatohepatitis. We diagnosed the patient with functional hyperthermia and proceeded to assess the mental and physical stressors for the same. Two months after the visit, we suspected OSAS as a stressor since the patient had a history of snoring and had gained more than 10 kg 1 year before the visit. Simple polysomnography revealed severe OSAS with an apnea–hypopnea index of 44.5; thus, continuous positive airway pressure (CPAP) was introduced during his sleeping hours at night. Subsequently, the patient's sleep time increased, his malaise disappeared, and the axillary temperature decreased gradually (Figure 1).

Table 1. Hematological and blood chemistry data of the patient collected at their first visit to our hospital.

Variable	Value
White blood cell count (/μL)	7980
Red blood cell count ($\times 10^4$/μL)	490
Hemoglobin (g/dL)	15.9
Platelet count (/μL)	221,000
Erythrocyte sedimentation rate (1 h/2 h; mm)	2/10
Blood urea nitrogen (mg/dL)	13
Creatinine (mg/dL)	0.86
Sodium (mmol/L)	142
Potassium (mmol/L)	3.8
Chloride (mmol/L)	106
Calcium (mg/dL)	9.5
Ferritin (ng/mL)	417
Uric acid (mg/dL)	4.5
Aspartate aminotransferase (U/L)	31
Alanine aminotransferase (U/L)	39
Alkaline phosphatase (U/L)	50
Lactate dehydrogenase (U/L)	215
Total bilirubin (mg/dL)	0.9
Amylase (U/L)	85
C-reactive protein (mg/dL)	0.18
Creatine phosphokinase (U/L)	76
Glucose (mg/dL)	117
Hemoglobin A1c (%)	6.5
IgG (mg/dL)	889
IgA (mg/dL)	261
IgM (mg/dL)	25
IgE (IU/mL)	11.7
C3 (mg/dL)	116
C4 (mg/dL)	35
CH50 (U/mL)	64.9
Thyroid-stimulating hormone (μIU/mL)	1.75
Free triiodothyronine (pg/mL)	3.22
Free thyroxine (ng/mL)	1.23
Cortisol (μg/dL)	8.75
Treponema pallidum latex agglutination automated test	Negative
Hepatitis B surface antigen	Negative
Hepatitis C antibodies	Negative
Procalcitonin (ng/mL)	0.08
Anti-cytomegalovirus IgG	Negative
Anti-cytomegalovirus IgM	Negative
Proteinase-3-antineutrophil cytoplasmic antibody	Negative
Myeloperoxidase–antineutrophil cytoplasmic antibody	Negative
Anti-cyclic citrullinated peptide antibody (U/mL)	<0.5
Anti-nuclear antibody	<40
Anti-double-stranded DNA antibody	Negative
Anti-SSA/Ro antibody	Negative
Anti-SSB/La antibody	Negative

C: complement; CH50: complement total; Ig: immunoglobulin; SSA: Sjögren's-syndrome-related antigen A; SSB, Sjögren's-syndrome-related antigen B.

Discussion

This case report highlights the following two important messages: (1) functional hyperthermia should be considered a possible cause of fever with a negative inflammatory response, and (2) OSAS can be a stressor for functional hyperthermia.

Regarding the first point, the opportunity to routinely monitor body temperature has increased with the COVID-19 pandemic.[5] An elevated body temperature leads to patient anxiety,

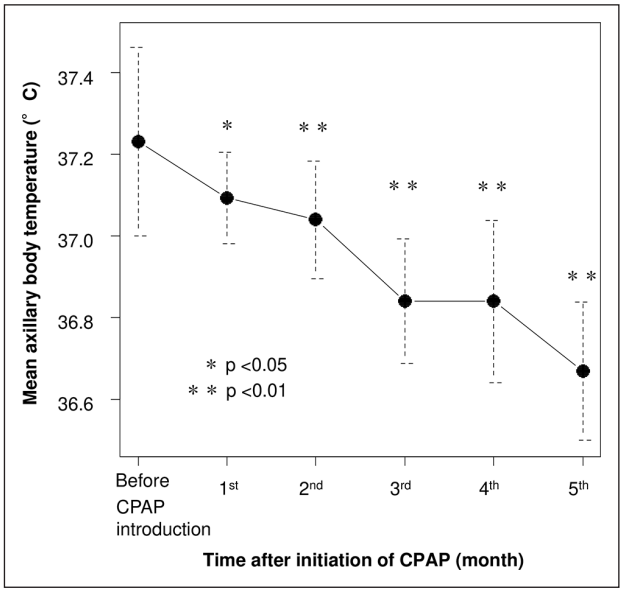

Figure 1. Mean axillary body temperature of the patient before and after initiating continuous positive airway pressure (CPAP). The patient's body temperature was measured at around 7:00 a.m. Compared to the axillary body temperature before the introduction of CPAP, the axillary body temperature after the introduction of CPAP was significantly decreased ($p < 0.01$, ANOVA; ** $p < 0.01$ or * $p < 0.05$, t-test with Bonferroni correction. All statistical analyses were performed using EZR version 1.54.). The mean axillary body temperature before CPAP is derived from data for 83 consecutive days before CPAP introduction. The mean temperatures for the first, second, third, fourth, and fifth months are derived from data for 1–28 days, 29–56 days, 57–84 days, 85–112 days, and 113–137 days, respectively.

limitation of social activities, and unnecessary medical visits.[6] Unlike pediatric or adolescent patients, adults with functional hyperthermia have a low-grade fever and are not highly anxious, agitated, or impulsive regarding their stressors.[1] In addition, functional hyperthermia is challenging to diagnose because no serological or imaging abnormalities are present. Central or drug-induced fever should also be ruled out, especially in adults. In some cases, the absence of abnormalities in laboratory and imaging studies may lead physicians performing a simple follow-up examination from the perspective of a psychogenic problem. However, if the patient's daily social life is disturbed, as in the present case, active diagnosis and treatment of functional hyperthermia are necessary. Treating functional hyperthermia in adults requires a multimodal approach that includes the treatment of comorbidities other than hyperthermia.[1] Specifically, this consists of explaining the disease to the patient, lifestyle guidance, environmental adjustments, verbal and non-verbal psychotherapy, psychophysiological techniques, pharmacotherapy, and treatment of comorbidities as necessary.[4] Medical providers must work with specialists according to the patient's condition.

Regarding the second point, OSAS is a sleep disorder characterized by complete or partial airway obstruction due to upper airway collapse during sleep, which then causes snoring and choking.[7] CPAP was effective in improving hyperthermia and malaise in our patient with severe OSAS. Patients with OSAS display significant sleep fragmentation, and chronic sleep fragmentation may elevate the body temperature. CPAP improves sleep consolidation and may, thus, restore the body temperature. Although the patient had diabetes, changes in weight and HbA1c levels were not associated with his body temperature. Malaise is a typical symptom of OSAS but not hyperthermia.[8] Therefore, it is reasonable to consider the role of OSAS as a stressor of functional hyperthermia in our case. Considering the significant interaction between sleep and thermoregulatory systems at various levels (from cellular to behavioral), the sleep quality itself could have been a risk factor for functional hyperthermia. Other common stressors in adult patients include primary headache, functional gastrointestinal disorders, psychophysiological insomnia, and adjustment and mood disorders.[4] Medications that could be used while treating patient comorbidities include central nervous system agents, such as benzodiazepines, histamine H1 receptor antagonists, serotonin 1A partial agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs),[4] beta-blockers (e.g. carvedilol),[9] and Japanese Kampo medicines (e.g. kami-shoyo-san).[4] Non-steroidal anti-inflammatory drugs are considered ineffective or of limited efficacy,[4] and SSRIs are less effective in adults.[1]

Conclusion

In conclusion, functional hyperthermia should be considered a cause of fever with a negative inflammatory response. OSAS can be a stressor for functional hyperthermia, which can be improved by interventions.

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Author contributions

H.M. conceived the idea and wrote the original draft of the manuscript. T.K. and T.A. developed the theory of this study. All authors discussed the case and commented on the manuscript. H.M., T.K., and T.A. revised and edited the manuscript. All authors gave final approval before submission of the manuscript.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

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Patient consent

Written informed consent was obtained from the patient for publication of this case.

Research ethics

Our institution does not require ethical approval for reporting individual cases or case series.

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