Positive Naproxen Test in Psychogenic Fever

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Pyrexia of unknown origin (PUO) broadly includes any febrile illness lasting ≥3 weeks with a temperature >38.3°C (100.9°F) on at least 2 occasions in the absence of a known immunocompromised state and an uncertain diagnosis after a thorough assessment including history taking, physical examination, and appropriate investigations.[1] PUO can be due to infectious, inflammatory, neoplastic, or other miscellaneous causes. Treatment with naproxen has been shown to result in lysis of fever within 24 hours in patients with PUO due to noninfectious causes, while patients with infectious conditions show little response.[2,3] Hence, the naproxen test has been proposed as a useful diagnostic tool to differentiate PUO of infectious from noninfectious, especially neoplastic, etiology. However, the low sensitivity and specificity of the naproxen test has limited its wider acceptability.[4] Psychogenic fever, also known as functional hyperthermia, is an underrecognized potential etiology of PUO.[5] Here, we report a case of PUO, in the context of acute stress and depression, with a positive naproxen test.

Case Report

A 57-year-old man presented to the emergency department experiencing fever with chills, rigors, and a mild headache for about 12 days and hiccoughs for 3 days. He had no other significant medical history. He was a smoker and had a history of hematologic malignancies in first-degree relatives. On examination, he was febrile (39.9°C/103.8°F). All other physical examination findings were normal. He was admitted to the hospital, and during the hospital stay he had persistent fever, which did not subside after treatment with acetaminophen. Considering the family history of hematologic malignancies, a week into the hospital admission, a trial of naproxen 500 mg was started, which resulted in complete lysis of fever after a single dose (positive naproxen test). He remained afebrile and was discharged 3 days after administration of naproxen. An extensive investigative workup revealed no potential cause of PUO. Full blood counts, liver function tests, kidney function tests, lipid profile, blood sugar level, C-reactive protein, erythrocyte sedimentation rate, and serum ferritin were within the normal range. Blood cultures for common bacterial infections were negative. Appropriate investigations for viral infections, like HIV and hepatitis B and C, were negative. Immunology panel to rule out inflammatory causes was negative. Tuberculin skin test was negative. Chest x-ray, ultrasound of the abdomen, and echocardiogram were nonremarkable. Magnetic resonance imaging of the brain was normal except for an incidental finding of a small hemangioma in the parietal area. Fluorodeoxyglucose–positron emission tomography to rule out any occult malignancies was negative.

During his stay in the hospital, he reported experiencing significant emotional disturbances and was referred for psychiatric evaluation. The psychiatric assessment revealed that he was experiencing low mood, anhedonia, hopelessness, crying spells, and impaired sleep and appetite for about a month. These symptoms were having a significant impact on his day-to-day functioning. Over a week after these symptoms had started, he developed fever with chills and rigors, which resolved with naproxen, but the mood symptoms persisted. These symptoms started following the death, over 7 weeks ago of two close relatives due to infectious encephalopathy. He was diagnosed with moderate depressive episode, according to *ICD-10* criteria, and psychogenic fever in the context of a significant stressful life event. He was prescribed agomelatine 25 mg daily as an antidepressant following the psychiatric assessment. On follow-up after 2 weeks, he showed improvement in his sleep, appetite, and mood. He had no further episodes of fever following discharge from the hospital.

Discussion

An increase in core body temperature has been reported due to psychological stressors.[6] Most patients with psychogenic fever show resolution of fever with psychotropic medications such as phenobarbitones and antidepressants such as selective serotonin reuptake inhibitors and tricyclic antidepressants but not with standard antipyretics. Animal models of depression associated with acute stressors show

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increase in body temperature up to 2°C (35.6°F). This elevation of temperature is attributed to release of pyrogenic interleukins (like IL-1) and proinflammatory prostaglandin E2 (PGE2), which act on the thermoregulatory preoptic nucleus of the hypothalamus. Animal models with chronic stressors that simulate depression are at least in part mediated by microglial activation and proinflammatory cytokines. Patients with depression have also been shown to have increased proinflammatory agents, which are hypothesized to have an etiopathologic role.[7] The efficacy of naproxen in PUO of noninfectious origin is thought to reflect its differential effect on pyrogenic substances, elaborated by noninfectious versus infectious causes. Lysis of psychogenic fever with naproxen is most likely due to attenuation of these pyrogenic agents, the levels of which would not be as high as in infectious diseases. We could not confirm this hypothesis in our patient, as we did not obtain the blood levels of proinflammatory cytokines/prostaglandins, though nonspecific inflammatory markers like CRP and ESR were within the normal range.

In conclusion, this case suggests that naproxen may be helpful in lysis of psychogenic fever in the background of significant stressors and depression; however, this needs further exploration through appropriately designed studies. The case also suggests the need for considering psychogenic fever as a potential differential diagnosis in the evaluation of PUO. Considering the current coronavirus disease 2019 pandemic and related stress, clinicians may encounter similar cases of psychogenic fever. The naproxen test may be a useful aid in the differential diagnosis of such patients.

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