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Sickness behavior may follow fracture as well as infection

Rachel Nicoll

Department of Public Health and Clinical Medicine, Umea University, Umea, SE-901 87, Sweden

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ABSTRACT

Sickness behavior, induced by pro-inflammatory cytokines in the early stages of an infection, is well known. A case report of three fracture patients, who were not taking analgesic medication, suggests that the initial symptoms experienced, particularly fatigue and mood changes, mirror those of the sickness behavior of infection. A mini-review only found studies investigating one physical, mental or emotional symptom in fracture patients and none drew a parallel with sickness behavior, suggesting that this is a hitherto unrecognised phenomenon which would benefit from further investigation.

1. Introduction

When a bone is fractured, the healing process normally begins with inflammation, with an immediate accumulation of blood cells adjacent to the injury site forming a haematoma, which acts as a template for callus formation (Mahamutha and Jothipriya, 2015). These cells release inflammatory mediators and increase the permeability of blood capillaries; this initial inflammatory reaction generally resolves within seven days. The five classic signs of inflammation (pain, heat, redness, swelling and loss of function) are well known but there may be other symptoms of inflammation which are not confined to the site of injury and not obviously connected with local healing processes. It is normal in cases of fracture for the patient to be prescribed or recommended to take analgesics, which can mask these natural symptoms of inflammation. This case report documents additional symptoms experienced by three fracture patients who took no analgesics, other medication or supplements designed to reduce pain or inflammation.

2. Findings

Three patients with fractures of differing severity and who had taken no analgesics, independently experienced a number of symptoms which had considerable concurrence. These are summarised in Table 1, which shows the patient questionnaire and their individual responses.

Patient 1, a female aged 50–59, had by far the most serious injury (double arm fracture and ligament damage), and also experienced the most numerous and prolonged symptoms. She craved sweet foods, which made her feel better, but unexpectedly lost weight during the first four weeks. She also felt feverish in the first week and developed swollen lymph nodes in the armpit of the fractured arm from the fourth week onwards. She became remarkably sensitive to temperature, experiencing cold during the first week, heat during weeks two and three and cold again thereafter. During the first four weeks she experienced fatigue, a symptom that was shared between all three patients. She also suffered memory loss and experienced difficulty concentrating from the time of the fracture onwards. There was a slight increase in incidence of headaches. During the first two weeks she experienced increased daytime sleepiness, but from the third week onwards she found extreme difficulty in getting to sleep, requiring night time snacking; unusually she awoke feeling unrefreshed. Her emotional state fluctuated, experiencing sadness and disappointment during the first two weeks, resignation in week three and was happy and excited thereafter.

Patient 2, a female aged 60–69 with a toe fracture, experienced many of the symptoms of Patient 1 but to a lesser extent and the symptoms were of shorter duration. Most of the symptoms were noticed in the first week, when she also experienced unexpected weight loss, cold, restlessness, inability to concentrate, fatigue, depression, increased incidence of headache and felt feverish. She also found that she needed to urinate more often in the first few days and needed to clear her throat of mucous more frequently during the first couple of weeks.

Patient 3, a male aged 50–59, suffered a stress fracture of the foot. He experienced many of the symptoms of the other two patients but attributed most of these to the direct result of the impact of the fracture on his life. Other than those, he experienced frustration during weeks one to eight, mild depression, low mood and lack of motivation during weeks two to six and reduced energy from weeks two to eight. He also developed frequent nosebleeds during weeks three to nine.

In summary, all three patients suffered increased fatigue/reduced energy at various stages of the healing process and all experienced mood changes, with the severity of the fracture indicating a longer duration and wider variability of symptoms.

E-mail addresses: rachelnicoll25@gmail.com, rachel.nicoll@umu.se.

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Table 1
Patient questionnaire and responses.

	Patient 1	Patient 2	Patient 3
Gender	Female	Female	Male
Age	50–59	60–69	50–59
Injury	Arm fracture x 2 and ligament damage	Toe fracture	Foot stress fracture
Food cravings?	Sweet foods, esp milk chocolate, weeks 1–8	No	No
Did eating make you feel better?	Yes, sweet foods weeks 1–8	No	No
Unexpected weight loss or gain?	Weight loss weeks 1–4	Weight loss week 1	No
Any swollen lymph nodes?	Yes, under broken arm from week 4 onwards	No	No
Any more or less sensitive to temperature?	More sensitive to cold week 1, hot weeks 2–3, cold week 4 onwards	Cold during first few days	No
Any change in fatigue or energy?	More fatigue weeks 1–4	Fatigue week 1	Reduced energy weeks 2–8
Restlessness, inability to focus or concentrate?	Yes, struggled to concentrate week 1 onwards	Yes, week 1	No
Memory loss, 'brain fog', dizziness?	Yes, time 0 onwards	No	No
Change in incidence of headaches or migraines?	Slight increase	Week 1	No
Change in difficulty sleeping unrelated to fracture pain?	Wide awake late at night week 1 onwards; required snacks at night	No	No
Slept for longer or less time?	Woke unrefreshed	No	No
Change in sleepiness during the day?	Very sleepy weeks 1–2; week 3 onwards wide awake, including late night	No	No
Altered emotions?	Sadness, disappointment weeks 1–2; resignation week 3; happy/excited week 4 onwards	Depressed week 1	Frustration weeks 1–8; mild depression, low mood, lack of interest or motivation weeks 2–6
Feverish?	Week 1	Week 1	No
Urinating more or less often?	No	More often, first few days	No
Did you need to blow your nose or clear your throat more frequently?	No	Cleared throat more frequently weeks 1–2	No
Any other unusual symptoms?	No	No	Frequent nosebleeds weeks 3–9

3. Literature review

Among the relatively few studies of these symptoms following fracture, are the following.

3.1. Lymphatic system

Szczesny et al. noted that clinically there appears to be no involvement of local lymph nodes and set out to investigate this using lymphoscintigraphy. In contrast, they found that in patients with closed fractures, tissue damage was followed by reaction in the localised lymphatic system with immune cell infiltrates manifesting as dilation in order to drain the fracture site. This was accompanied by enlargement of inguinal lymph nodes, which persisted even after fracture healing. They commented that this provided evidence for the existence of a functional axis between the bone and surrounding soft tissue and the local lymphatic system and hypothesised that fracture gap tissue is the source of signals to the lymph nodes, releasing cellular and humoral regulatory factors. Healing is then regulated by influx into the bone fracture site of lymph node regulatory cells, with scavenger cells removing cellular debris from the damaged tissue and blood cells to the lymph nodes, likely resulting in swelling (Szczesny et al., 2007).

3.2. Temperature

Cold intolerance is a phenomenon known to develop and persist with hand injury (Nijhuis et al., 2010), but does not appear to have been assessed in any other type of injury.

3.3. Sleep disturbance

A study of 1095 patients with various fracture types showed that at three month follow up, many patients had experienced sleep difficulty, but this correlated with 12-month mental and emotional status rather than extent of functionality of the fractured limb (Shulman et al., 2015).

3.4. Depression

In an observational study of 296 females, the odds ratio for depression 12 months after a limb fracture was more than threefold higher among those aged over 65 than for younger women (Williams et al., 2014).

3.5. 'Sickness behavior'

Studies of infection, allergic asthma, hypoxia and immune-stimulants such as lipopolysaccharide have demonstrated many of the effects observed in these three patients, which have been grouped together as 'sickness behavior'. Sickness behavior is the result of the action of pro-inflammatory cytokines, which are released as part of the acute phase response. It can comprise symptoms such as loss of appetite, sleepiness, depression, lethargy, withdrawal from normal social activities, anhedonia, decreased libido, disturbed sleep, decreased memory and reaction time, weight loss, fever, aching joints and fatigue (Kozak et al., 2006; Dantzer and Kelley, 2007; Shattuck and Muehlenbein, 2016).

For some years, it was thought that 'sickness behavior' was pathological, with antipyretics recommended to reduce fever. Nevertheless, clinical trials are inconclusive on their benefits and antipyretics are known to increase mortality. More recent thinking is that the fever, as well as the psychological and behavioral components of 'sickness behavior', represent a highly organised strategy to fight infection which promotes energy conservation, slowing the replication of the infectious agent. Since many of the sickness behavior symptoms originate in the brain, it is thought that there is cross-talk between the immune system and central nervous system via the vagus nerve as an adaptive response to infectious micro-organisms to allow priority to be given to healing rather than maintenance of normal life (Konsman et al., 2002; Harden et al., 2015).

Since the 'macrophage theory of depression' was first described in 1995 as a manifestation of the acute phase response (Maes et al., 1995), there have been a number of studies specifically investigating the depression resulting from elevated pro-inflammatory cytokines. A meta-analysis of 24 studies found that several pro-inflammatory cytokines were elevated in major depression (Dowlati et al., 2010), while another showed that depression and fatigue were the most common symptoms of infection-induced cytokine increase, but may be modulated by age (Shattuck and Muehlenbein, 2016). This type of depression may be non-responsive to anti-depressants but may respond to anti-inflammatories (Kiecolt-Glaser et al., 2015; Miller and Raison, 2016; Wohleb et al., 2016).

4. Conclusion

This case study suggests that fracture can induce similar physical, mental and emotional responses in patients who have taken no analgesics. While there are very few studies investigating these symptoms following fracture, they do fall into the category of 'sickness behavior' which can be induced by infection. Induction of sickness behavior appears to account for many of the symptoms found in our case study: daytime sleepiness, depression, fever, weight loss and fatigue. The common factor here is pro-inflammatory cytokines, which are known to be elevated in both fracture and infection healing. While a cytokine-induced increase in core body temperature during fever might be beneficial in helping to kill infectious microorganisms, that is clearly not the mechanism of effect in fracture, indicating that some other process is at work. As it is not generally recognised that fracture can induce 'sickness behavior', this suggests scope for further observational studies.

Declaration of competing interest

The author declares no conflict of interest.

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