Brief Reports

Fatigue in Mastocytosis: A Case Series

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ABSTRACT

Purpose: Accumulating evidence suggests that fatigue in chronic inflammatory diseases is generated in the brain by mechanisms involving proinflammatory cytokines. We recently reported a high prevalence of fatigue in patients with mastocytosis, a condition with a constant activation of mast cells and release of a variety of bioactive substances. This observation indicates that mast cells somehow could be involved in the biological mechanisms that generate fatigue. In this case series, we aim to describe how typical triggering factors of mastocytosis attacks, as reported by patients, are accompanied by increased fatigue. Possible mechanisms by which mast cells may contribute to the pathophysiology of fatigue are discussed.

Methods: Seven patients with mastocytosis were interviewed regarding triggers and clinical symptoms and signs of mastocytosis, including the presence and severity of fatigue. Fatigue severity during and between attacks was assessed using the fatigue Visual Analog Scale (fVAS).

Findings: The most important reported triggers were heat and/or cold, exercise, food, alcohol, and psychological stress. The median fatigue Visual Analog Scale scores were 80 (range 40–91) during attacks and 40 (range 30–72) between attacks Fatigue reportedly impaired social and recreational activities in all 7 patients, and influenced occupational activities in 6.

Implications: This case series illustrates that fatigue is common and severe among patients with mastocytosis. Fatigue increases during attacks, which may indicate that mast cell–derived substances are directly involved in the pathophysiology of fatigue. Mast cells could be an underestimated cellular actor in fatigue and other conditions and thus may represent a potential therapeutic target. (*Clin Ther*. 2019;41:625–632)

Keywords: activities of daily living, fatigue, mast cells, mastocytosis, quality of life.

INTRODUCTION

Mast cells are innate immune cells found in all human tissues. They respond rapidly to a variety of invading pathogens and dangers and serve as major effector cells in allergic reactions.[1] On activation, mast cells release a multitude of biologically active substances, including proinflammatory cytokines, proteases, and vasoactive peptides.[2]

Mastocytosis refers to a group of disorders characterized by excessive accumulation of clonally expanded mast cells in one or more tissues.[3,4] The pathogenesis most commonly involves gain-of-function mutations in the *KIT* proto oncogene encoding the receptor tyrosine kinase protein CD117, resulting in unopposed differentiation, survival, and activation of mast cells.[3,5] Uncontrolled activation causes an excessive release of biologically active mediators, resulting in a variety of dermatologic, cardiovascular, gastrointestinal, and constitutional signs and symptoms.[3] It is increasingly recognized that the CNS is also affected, and many patients experience problems with concentration and memory, as well as other neurologic and cognitive disturbances.[6–11] This subjective disturbance of consciousness is popularly referred to by some patients as "brain fog."[12]

Fatigue has been recognized as a prevalent phenomenon in most chronic inflammatory diseases,

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but has gained relatively little attention in mastocytosis research. *Chronic fatigue,* defined as "an overwhelming sense of tiredness, lack of energy and feeling of exhaustion,"[13] is a potentially disabling phenomenon often accompanying chronic inflammatory diseases, neurodegenerative disorders, and cancer.[14] It represents a substantial element of the *sickness behavior response,* an evolutionary, highly conserved survival strategy characterized by fatigue; psychiatric depression; and loss of thirst, appetite, and grooming, observed in all animals, including and humans, during infection, bodily damage, or on exposure to other factors that activate the innate immune system.[15] Although the pathogenesis of fatigue is much debated and only partly understood, accumulating evidence supports a role for innate immune system activation with the release of proinflammatory cytokines, particularly interleukin (IL)-1β.[16] According to this concept, fatigue is generated in the brain and influences a variety of human life dimensions.

We recently reported remarkably severe and prevalent fatigue in a group of patients with mastocytosis.[17] The observation may indicate an underestimated role for mast cells in the pathogenesis of fatigue. This may not be the case only in mastocytosis but also in other diseases characterized by chronic activation of innate immunity, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis. In light of the lack of effective treatment options for fatigue, mast cells could represent a potential therapeutic target.

In this article, we present further data that describe the relationship between mastocytosis and chronic fatigue, and illustrate how different triggers of mast cell activation generate or exacerbate fatigue.

MATERIALS AND METHODS

Patient–members of the Norwegian Association for Patients with Mastocytosis (*Mastocytoseforeningen*) were invited to participate in an interview regarding triggers and clinical symptoms and signs of mastocytosis, including the presence and severity of fatigue. Fatigue was measured with the Fatigue Visual Analog Scale, a widely used and accepted generic and unidimensional instrument for subjective scoring of fatigue. Scores range from 0 to 100, with higher numbers corresponding to more severe fatigue.[18] Patients were also asked to report which symptom(s) most severely affected their quality of life. All participants provided informed consent. The study protocol was approved by the Regional Committee for Medical and Health Research (REK Vest 2010/1455).

RESULTS

The results of the interviews are summarized in the Table. Seven patients participated in the survey, 4 with indolent systemic mastocytosis and 3 with cutaneous mastocytosis. Six of the respondents (85.7%) were women, and the median age was 47 years (range, 35–64 years).

The most important triggers reported spontaneously by the patients were heat and/or cold, exercise, food, alcohol, and psychological stress. Five patients reported psychological stress as the most severe trigger of attacks. All patients reported pruritus, urticaria, flushing, bloating, fatigue, as well as impaired memory and concentration during attacks. The median fatigue Visual Analog Scale scores were 80 (range 40–91) during attacks and 40 (range 30–72) between attacks. Fatigue reportedly impaired social and recreational activities in all 7 patients, and influenced occupational activities in 6. Five patients (71.4%) answered "fatigue" when asked which symptom most severely affected their quality of life.

DISCUSSION

This case series illustrates that fatigue is a common and severe manifestation of cutaneous and systemic mastocytosis, and increases markedly during attacks when mast cell activation takes place. Between patients, triggers of attacks varied, but comprised several well-known stimuli of mast cell activation, including temperature (heat and/or cold), food, as well as physical and psychological stress. Increased fatigue was a dominant feature regardless of the stimuli that triggered the event.

Mastocytosis can be considered an illustrative model of the biological mechanisms that generate fatigue. The disease is characterized by a continuous release of mast cell–derived mediators such as proinflammatory cytokines, histamine, proteases, vascular endothelial growth factor, as well as other highly bioactive substances.[3] Occasionally, patients experience attacks with massive mast cell activation and the release of mediators. The attacks are triggered by exposure to stimuli that are known to activate mast cells, and are characterized by a rapid

Table. Patients' characteristics.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Diagnosis	Indolent SM	CM	CM	Indolent SM	Indolent SM	Indolent SM	CM
Sex	Female	Female	Female	Male	Female	Female	Female
Age, y	44	47	35	43	64	64	52
Triggers	Heat and cold, exercise, food, odors,	Heat, exercise, food, alcohol, psych. stress	Heat and cold, exercise, food, alcohol, psych. stress	Heat, exercise, food, psych. stress	Heat and cold, exercise, food, alcohol, psych. stress, odors, anesthesia	Heat, exercise, psych. stress	Cold, exercise, food, alcohol, psych. stress, odors, anesthesia, insect bites
Worst trigger	Food	Psych. stress, exercise	Heat	Psych. stress	Psych. stress	Psych. stress, heat	Psych. stress
Symptoms							
System affected							
Skin	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing	Pruritus, urticaria, flushing
Gastrointestinal	Abd. pain, bloating	Abd. pain, bloating, nausea	Abd. pain, bloating, nausea, diarrhea	Abd. pain, bloating, diarrhea	Abd. pain, bloating, nausea, vomiting, diarrhea	Bloating, nausea	Bloating, nausea, diarrhea
Cardiovascular	Dizziness, presyncope	Dizziness	Syncope	Dizziness, presyncope	Dizziness, presyncope	Dizziness	Dizziness
Central nervous system	Fatigue, impaired memory, impaired concentration	Fatigue, irritability, mood swings, impaired memory,	Fatigue, irritability, mood swings, impaired memory,	Fatigue, impaired memory, impaired concentration	Fatigue, irritability, impaired memory, impaired concentration	Fatigue, impaired memory, impaired concentration	Fatigue, impaired memory, impaired concentration

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Table. (*Continued*)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
		impaired concentration	impaired concentration				
Other symptoms		Arthralgia, myalgia	Arthralgia, myalgia		Arthralgia, myalgia	Myalgia	Arthralgia, myalgia
Symptoms that most severely affect QoL	Fatigue	Fatigue, arthralgia, myalgia	GI symptoms	Fatigue	Fatigue, arthralgia, myalgia, dizziness	Fatigue, flushing	Fear of attacks
Fatigue							
Fatigue during attacks (fVAS)	90	91	79	70	88	40	80
Fatigue between attacks (fVAS)	64	57	40	40	72	30	30
Activities with which fatigue interferes	Social, occupational, recreational	Social, occupational, recreational	Social, occupational, recreational	Social, occupational, recreational	Social, recreational	Social, occupational, recreational	Social, occupational, recreational

abd. = abdominal; CM = cutaneous mastocytosis; GI = gastrointestinal; fVAS = Fatigue Visual Analog Scale; psych. = psychological; QoL = quality of life; SM = systemic mastocytosis.

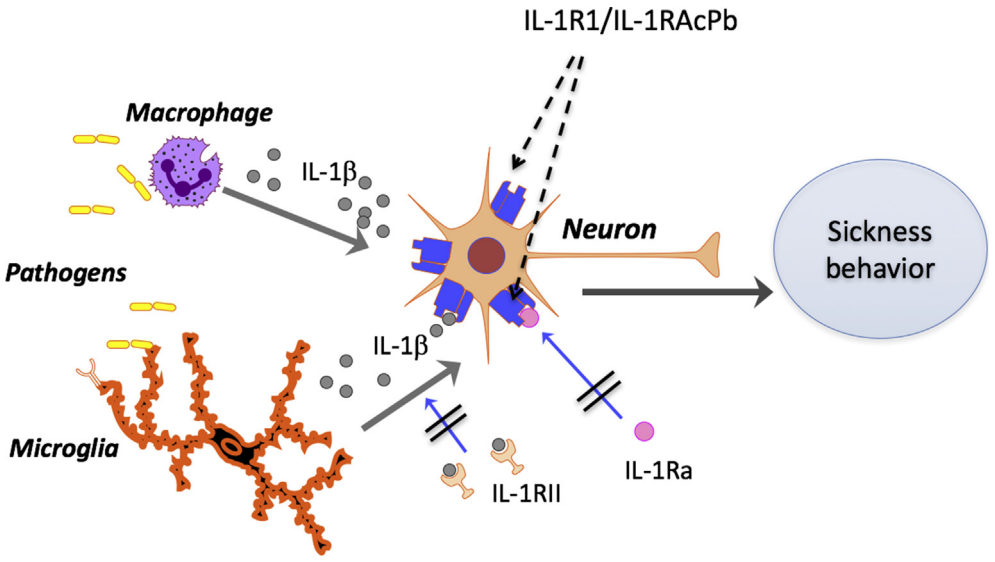

Figure 1. The sickness behavior response. Interleukin (IL)-1β from activated macrophages and/or microglia bind to the signaling complex of IL-1 receptor type I (RI) and the brain isoform of the accessory protein IL-1RAcPb on neurons, and induce fatigue (sickness behavior). IL-1β signaling is down-regulated by interleukin-1 receptor antagonist (Ra) and by soluble IL-1 receptor II (RII).

development of a variety of clinical signs and symptoms that can be directly related to the chemical and biological functions of mast cell–derived factors.[3,5] Of note, among these are bioactive substances such as proinflammatory cytokines that are well known to be crucial for inducing sickness behavior response.[19]

Sickness behavior is a subconscious and automated behavior characterized by sleepiness; depressed mood; and loss of grooming, thirst, appetite, and initiative, and is thought to increase survival during temporary infections and bodily harm.[16,20] It is evolutionary, strongly conserved, and occurs in all animals, including humans. Fatigue constitutes a considerable part of this response.[15,16] However, in conditions and diseases with chronic inflammation or cellular stress, fatigue becomes chronic and seems to serve no adequate purpose. Substantial evidence from animal studies shows that IL-1β is essential for the generation of sickness behavior; this process can be abrogated by IL-1 receptor antagonists and has been reported not to occur in *IL-1R* knockout mice.[19] In humans, treatment with IL-1–blocking agents has been reported to alleviate fatigue.[21,22]

When innate immune cells such as macrophages are activated by invading pathogens or other dangers, proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor α (TNF-α) are released. IL-1β enters the CNS through active and passive transport over the blood–brain barrier, and is also produced by microglia in the brain through vagal stimulation.[23] Once inside the brain, IL-1β binds to a subtype of the IL-1 receptor type I (IL-1RI) and to a brain isoform of the accessory protein IL-1RaAcPb on neurons[24] (Figure 1). These interactions directly modify synaptic transmission through neuronal potassium and calcium influx, resulting in altered neurotransmission, inducing subconscious and irresistible sickness behavior.[25] Many of the inflammatory mediators released from activated mast cells in the periphery pass the blood–brain barrier and activate brain-resident mast cells. Even more inflammatory mediators thus appear intrathecally, and IL-1β bind to the IL-1RI/IL-1RaAcPb complex on neurons and induce sickness behavior and fatigue (Figure 2).

Through evolution, mast cells have developed the ability to combat a large variety of pathogens and

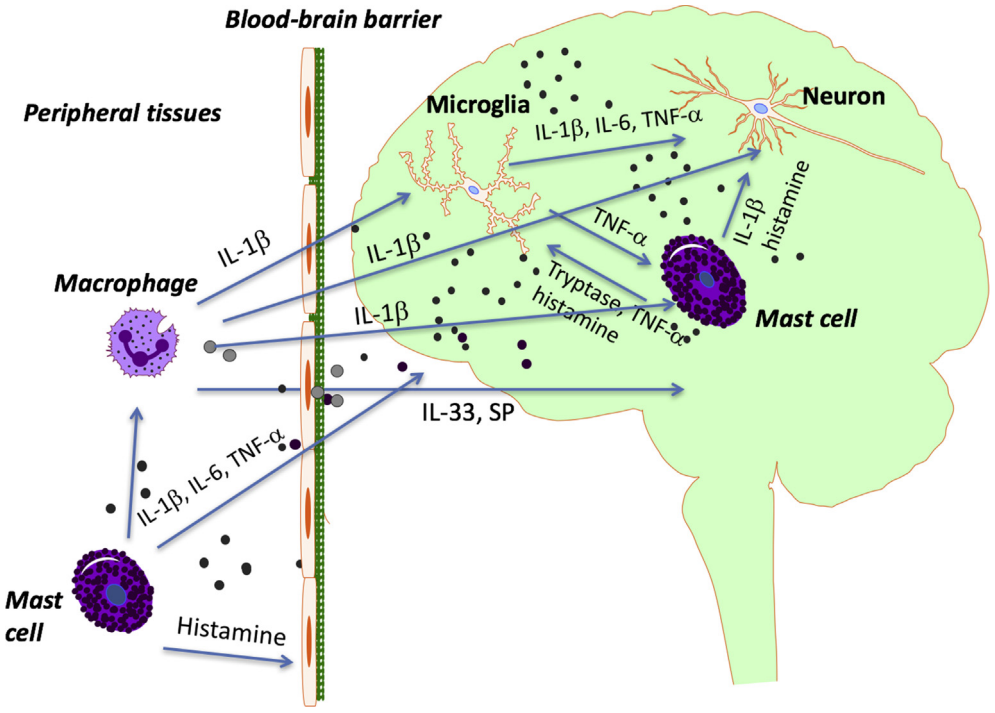

Figure 2. A molecular model for fatigue in mastocytosis. Mast cells both in the periphery and in the brain produce and secrete pro-inflammatory cytokines, histamine, proteases, substance P (SP), and other highly active signaling and reactive substances. Macrophages in the periphery and microglia in the brain become activated and produce interleukin (IL)-1β and other proinflammatory substances. IL-1β binds to receptors on cerebral neurons and induce the sickness behavior response, in which fatigue is a major element. Vascular endothelial growth factor disrupts the blood–brain barrier and augments influx to the brain of immune cells, cytokines, and other signaling molecules. IL-33 and SP together strongly increase IL-1β release from mast cells. TNF-α = tumor necrosis factor α.

dangers. Mast cell activation can thus be induced by a plethora of triggers such as allergen-specific high-affinity receptor for the Fc region of immunoglobulin E (FcεRI), pattern-recognition receptors, G-protein–coupled receptors, nuclear receptors, and alarmin receptors.[2] Trigger activation takes place in patients with mastocytosis or other disorders characterized by mast cell hyperfunction. In this case series, all of the patients reported that what they recognized as mast cell attacks were accompanied by increased fatigue, and fatigue could precede the onset of other symptoms as well as persist for hours or days following the resolution of accompanying symptoms. Characteristic triggers were heat and cold, exercise, food, alcohol, and psychological stress.

The exact molecular interactions between the insult and activation of mast cells are incompletely understood. Heat and cold are well-known triggers, but little is known about the triggering biological mechanisms. One study in mice demonstrated increased mast cell degranulation in low temperatures,[26] but otherwise one could speculate whether some unidentified temperature-responsive alarmin could be involved. IL-33 is a powerful activator of mast cells and is released immediately from endothelial cells, fibroblasts, and epithelial cells in contact with the environment during various dangerous situations, and could hypothetically be such an actor.[27–29]

Exercise, friction, and scratch are also commonly reported as triggers of mastocytosis attacks. Mast

cells respond to danger signals emitted by injured tissues or cellular stress. Mechanical trauma, infections, radiation, toxins, and ischemia trigger the release of alarmin IL-33 and represent a possible link to activation.[30,31]

Furthermore, psychological/emotional stress is a common trigger of mast cells and illustrates how the nervous system and immune system are closely integrated in defending life. There are speculations that corticotropin-releasing hormone released during stress activates mast cells.[3] Also nerve growth factor released into the bloodstream can induce mast cell degranulation in adult male mice.[32] Substance P, neurotensin, and nerve growth factor activate mast cells by direct G-protein binding or by ligand binding, for example to neurokinin-1 receptor,[33] and represent additional hypothetical explanations for well-known clinical experiences that lack a solid theoretic basis. Psychological stress was reported to be the most powerful triggering factor in the majority of the patients in our case series.

With regard to the other triggering factors reported by these patients, no specific molecular signaling reasonably explains the activation mechanisms. However, the consistent reports by the patients and the associated increase in fatigue severity during the attacks, regardless of the triggering factor, indicate that mast cells have a central role in the biological mechanisms of fatigue. These observations underline the neurobiological role of mast cells in the pathogenesis of fatigue, and should be further studied not only in mastocytosis but also in other disease entities associated with innate immune system activation and fatigue.

There is a complex network of pro- and antiinflammatory cytokine signaling, as well as other factors, that regulate inflammatory activity.[31] While TNF-α, IL-1β, and IL-6 are classic drivers of inflammation, it has become clear that also the alarmin IL-33 is a strong inducer of inflammation and is produced by a variety of innate immune cells and other cell types. IL-33 activates mast cells and other immune cells, participates in allergic reactions, and can also be induced by direct IL-1 activation of mast cells.[28] Downregulation and termination of immune and inflammatory activity are important in controlling such reactions. IL-37 represents a strong down-regulator and is expressed by immune and nonimmune cells after proinflammatory stimuli. It particularly suppresses IL-1–mediated signaling, and is thus a natural regulator of innate immunity.[28]

CONCLUSIONS

Based on the findings from the present study, as well as the emerging understanding that mast cells are essential players in a wide array of innate immune responses, we hypothesize that the manipulation of mast cell activation and release of proinflammatory cytokines could represent a therapeutic option for fatigue. IL-37, IL-1 inhibition, and other down-regulators of mast cell activation are interesting options that need to be explored with future trials.

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Both of the authors contributed equally to the conceptualization, data collection, analysis, and writing of the manuscript. Both of the authors approved the final manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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