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**Review Article**

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# Long COVID neuropathy: The role of mast cells

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## ABSTRACT

Postacute sequelae of SARS-CoV-2 infection (PASC), or Long COVID, is estimated to affect over 60 million individuals globally, with almost half of COVID-19 survivors experiencing persistent symptoms such as neuropathic pain, fatigue, and autonomic dysfunction. Despite its prevalence, the pathophysiology of PASC remains poorly understood. This narrative review highlights activation of mast cells (MCs), the unique tissue immune cells as a central contributor to neuropathic manifestations in PASC. Mast cell locations near nerves and vessels allows them to regulate neuroimmune and neurovascular processes. Mast cell activation mirrors patterns seen in small-fiber neuropathy and myalgic encephalomyelitis/chronic fatigue syndrome, suggesting a shared immune-mediated etiology. The SARS-CoV-2 spike protein has been shown to activate MCs via angiotensin-converting enzyme 2 and toll-like receptor 4, triggering release of pro-inflammatory and neurotoxic mediators, including interleukin-1β, interleukin-6, tumor necrosis factor alpha, histamine, and tryptase. Such mediators sensitize peripheral nerves, disrupt the blood-brain barrier, and recruit microglia, ultimately contributing to small-fiber injury, neuroinflammation, and dysautonomia. Emerging reports suggest benefit from MC-directed treatments although responses remain variable. Understanding the role of MCs in PASC may offer a plausible mechanism of pathogenesis and guide targeted therapies. Future studies are needed to validate these findings and improve PASC patient outcomes.

**KEYWORDS:** COVID; flavonoids; mast cells (MCs); neuropathy; pain; treatment

## INTRODUCTION

Postacute sequelae of SARS-CoV-2 infection (PASC), also known as Long COVID syndrome, is the persistence of symptoms following COVID-19 infection. The World Health Organization (WHO) defines PASC as the presence of symptoms that persist for at least 2 months following SARS-CoV-2 infection and cannot be explained by an alternative diagnosis.[1] Over 60 million individuals globally, including 15-20 million in the United States, are affected by PASC.[2] A recent meta-analysis of prospective studies, involving over 480 000 individuals, found that more than half of COVID-19 survivors continued to experience at least 1 symptom related to PASC for more than a year after initial infection.[3] Similarly, a 2025 preprint meta-analysis of 429 studies, including over 2 million individuals with confirmed COVID-19 infection, reported a pooled global PASC prevalence of 36%.[4] Despite its global prevalence, the underlying mechanism of PASC remains unknown, with current hypotheses failing to fully account for the heterogeneous and multisystemic nature of the syndrome.

Postacute sequelae of SARS-CoV-2 has been implicated in numerous symptoms that impact multiple organ systems and one further triggered by physical exertion, mental activity, and emotional stress.[2,5] Fatigue is the most commonly reported symptom, followed by "brain fog" or cognitive dysfunction, other neuropsychiatric symptoms, dyspnea, chest pain, myalgia, and diffuse sensitivities (Figure 1).[6–11] Some new-onset conditions associated with PASC include neuropathic pain, cardiovascular disease, fibromyalgia, interstitial lung disease, and autoimmune disorders, especially myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and mast cell activation syndrome (MCAS).[2,12–16] Recent studies report peripheral neuropathy and myopathy in 26%-56.3% among patients suffering PASC.[17,18] In a large preprint cohort of 977 individuals with PASC, neuropathic symptoms were reported in 55% of participants.[19] Interestingly, many of the symptoms implicated in PASC resemble those presented by patients diagnosed with MCAS.[16] Therefore, involvement of mast cells (MCs) could be an underlying mechanism for the unknown pathogenesis of PASC.

Mast cells are typically activated by allergic triggers but they can also be triggered by pathogen-associated molecular patterns via activation of toll-like receptors (TLRs).[20,21] In addition, SARS-CoV-2 spike proteins were found to activate MCs by binding to angiotensin-converting enzyme 2 (ACE2) on their surface.[22–24] Activated MCs were recently detected in the lungs of deceased patients with COVID-19 and were linked to pulmonary edema, inflammation, and thromboses.[25,26] Due to the role MCs may play in both neuropathy and PASC, there is a need to further explore MCs as a possible therapeutic target in the treatment of PASC-related neuropathy. Thus, the aim of this article is to review the possible

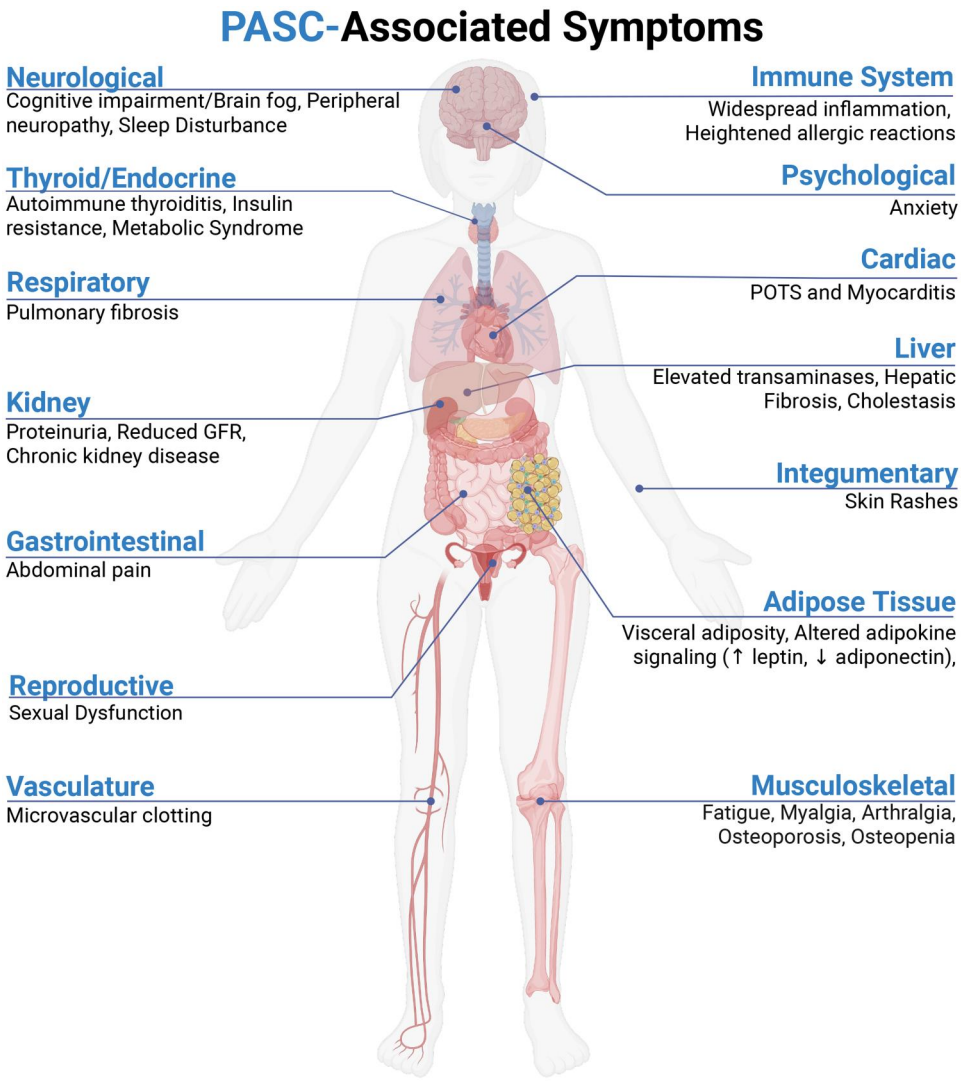


**Figure 1.** Diagrammatic representation of organ symptoms associated with postacute sequelae of SARS-CoV-2 infection (PASC). Created using BioRender.

role of MCs in the development and severity of neuropathic symptoms associated with PASC, different than those of inherited neuropathies, and explore treatment strategies to mitigate the chronic burden experienced by affected patients.[27] We hypothesize that chronic MC activation by COVID-19, along with the associated physical and mental stress, contributes to the development and persistence of neuropathic symptoms in individuals with PASC.

## METHODS

A narrative literature review was conducted using PubMed, Google Scholar, and Web of Science with the following keywords: "Mast cells" AND "neuropathy" OR "small fiber neuropathy" OR "nerve injury" OR "neuroinflammation." The search was not restricted by publication year but was limited to original articles published in English. Eligible studies directly investigated the role of MCs in the development or progression of neuropathy and the implication of MCs in PASC. We included both preclinical studies (in vitro and animal models) and clinical research (case reports, case series, and observational studies). Studies that did not address the role of MC in neuropathies or were not relevant to the topic of interest were excluded. The level of evidence for studies cited were categorized as low, moderate, or high based on study design, outcome objectivity, and the level of inference supported. Mechanistic or hypothesis generating data, such as in vitro and animal models, were considered low level of evidence; observational human studies, such as cross-sectional or retrospective analyses, were considered moderate level of evidence; and studies providing temporal or causal inferences, such as prospective cohorts or interventional designs, were considered high level of evidence. No formal risk of bias assessment was performed.

## RESULTS

### Neuropathy in PASC

Neuropathy has emerged as a significant symptom of PASC and has been found to involve small fibers, autonomic nerves

and, in a rare case, large fibers. Small-fiber neuropathy (SFN) is the most reported neuropathy in PASC patients. Oaklander et al. demonstrated that approximately 59% of PASC patients showed abnormalities consistent with SFN.[28] Two additional studies found that approximately 50% of PASC patients met diagnostic criteria for SFN based on biopsy and quantitative sensory testing.[29,30] Falco et al. also reported that incidence of SFN was unrelated to demographic or infection severity variables, emphasizing the need for universal screening of PASC patients presenting with pain.[29] Bitirgen et al. reported corneal small nerve fiber loss and increased dendritic cells in patients with PASC, especially those with neurological symptoms. Barros et al. evaluated 23 patients who recovered from COVID-19: over 90% of these patients presented with alterations of the corneal subbasal plexus and corneal tissue consistent with SFN.[31] Midena et al. assessed 151 patients and identified damage to small fibers secondary to SARS-CoV-2 infection, even after acute phase recovery.[32] Novak et al. reported SFN in PASC patients, with findings of reduced intraepidermal nerve fiber density and associated sensory abnormalities.[33,34] Panagiotides et al. presented a case of autoimmune SFN in a PASC patient who developed burning pain and numbness in all limbs following COVID-19 infection; sural nerve biopsy confirmed small-fiber axonal loss.[35] Burakgazi also reported 2 PASC patients who developed new-onset paresthesia and burning pain within weeks of COVID-19, with skin biopsy confirming SFN.[36] McAlpine et al. conducted a case-control study of 16 patients with PASC-associated SFN. These patients presented with distal burning pain, paresthesia, allodynia, orthostasis, and heart rate lability. Furthermore, 92% of participants reported postexertional malaise, and 89% met diagnostic criteria for ME/CFS. Patients experienced significant symptom improvement following immunotherapy.[37] Bandinelli et al. reported that multiple PASC patients who developed SFN presented with distal burning pain, numbness, joint swelling, and functional impairment over a long-term follow-up.[38] In addition, a large preprint observational study of 977 PASC patients reported neuropathic symptoms in 55% of participants (534/977). Among those who underwent skin biopsy, SFN was confirmed in 56.5% (48/85) of cases, with involvement of both epidermal and autonomic nerve fibers.[19] The limitation of conventional nerve conduction studies is that they primarily assess only large myelinated fibers and cannot detect pathology affecting small fibers.[39] Min et al. demonstrated that dermal nerve fiber biopsy can accurately distinguish clusters of immune-mediated neuropathies based on their underlying nodal, paranodal, and internodal pathology.[40]

Autonomic dysfunction often coexists with SFN. One study reported on 27 PASC patients who underwent autonomic testing. The most common clinical presentation associated with PASC was orthostatic symptoms without tachycardia or hypotension (41%), followed by postural orthostatic tachycardia syndrome (POTS) (22%), and borderline orthostatic intolerance (11%).[41] Multiple studies have reported autonomic dysfunction in PASC patients, with variable responsiveness to intravenous immunoglobulin (IVIG) treatment.[28,34,37,42] Additionally, 1 study compared PASC and ME/CFS patients, reporting a high prevalence of POTS, inappropriate sinus tachycardia at rest, and prolonged heat stimulus latency, which is suggestive of unmyelinated fiber damage.[43]

Large fiber neuropathies in PASC can also be present. Raahimi et al. reported a previously healthy 46-year-old man who was diagnosed with Guillain-Barré syndrome 53 days following SARS-CoV-2 infection. He presented with rapidly progressive lower motor neuron weakness involving all limbs, face, and respiratory muscles, which required the patient to be admitted to the intensive care unit for ventilatory support and IVIG treatment. Nerve conduction studies confirmed acute inflammatory demyelinating polyradiculoneuropathy.[44] In addition, Abu-Abaa et al. reported an 84-year-old patient who developed bulbar-onset amyotrophic lateral sclerosis (ALS) shortly after recovering from COVID-19. The patient initially presented with respiratory failure due to COVID-19 and was discharged after improvement. However, within a month he developed symptoms consistent with ALS including progressive dysphagia, dysarthria, bulbar weakness, bilateral facial weakness, hyporeflexia, and tongue fasciculations. Nerve conduction studies and electromyography supported the patient's ALS diagnosis.[45] These reports demonstrate the diverse spectrum of neurological manifestations observed in PASC.

## MCs in neuropathies

While neuroimmune dysregulation is increasingly recognized as a central mechanism, evidence suggests that MCs may serve as primary initiators of this process.[46] Mast Cells are sentinel immune cells widely dispersed throughout tissues that react to various triggers including immunoglobulin E (IgE), microbial products, neuropeptides, and cytokines. When stimulated, MCs can release neurohormonal, proinflammatory, tissue remodeling, and vasoactive mediators that exert both immunostimulatory and immunosuppressive actions.[47–55] Their perineural and perivascular localization, along with their neuroinflammatory capacity, identifies MCs as a critical link between SARS-CoV-2 infection and the development of neuropathic symptoms in PASC (Figure 2).[48,49,56,57]

Mast Cells have been implicated in the pathophysiology of various neuropathic syndromes.[58] Mast Cells are located in perivascular and perineural regions and contribute to nerve remodeling, demyelination, and subsequent neuropathic pain (Figure 3). Brum et al. found MC accumulation in fibromyalgia mouse models that developed allodynia and muscle fatigue. These clinical manifestations were prevented by pharmacological MC depletion.[59] Castells et al. reported the presence of SFN in patients with systemic mastocytosis.[54] Mast Cells were also implicated in complex regional pain syndrome (CRPS), another neuropathic disorder. Morellini et al. studied skin biopsy of patients with CRPS and found significant reduction in dermal nerve fiber density in CRPS-affected limbs but with no correlation to disease duration. In addition, the total percentage of MCs was consistent between affected and unaffected patients compared to the healthy patients. However, the study found MCs located within 5 μm of the nerve fibers to be significantly lower, which led authors to propose that

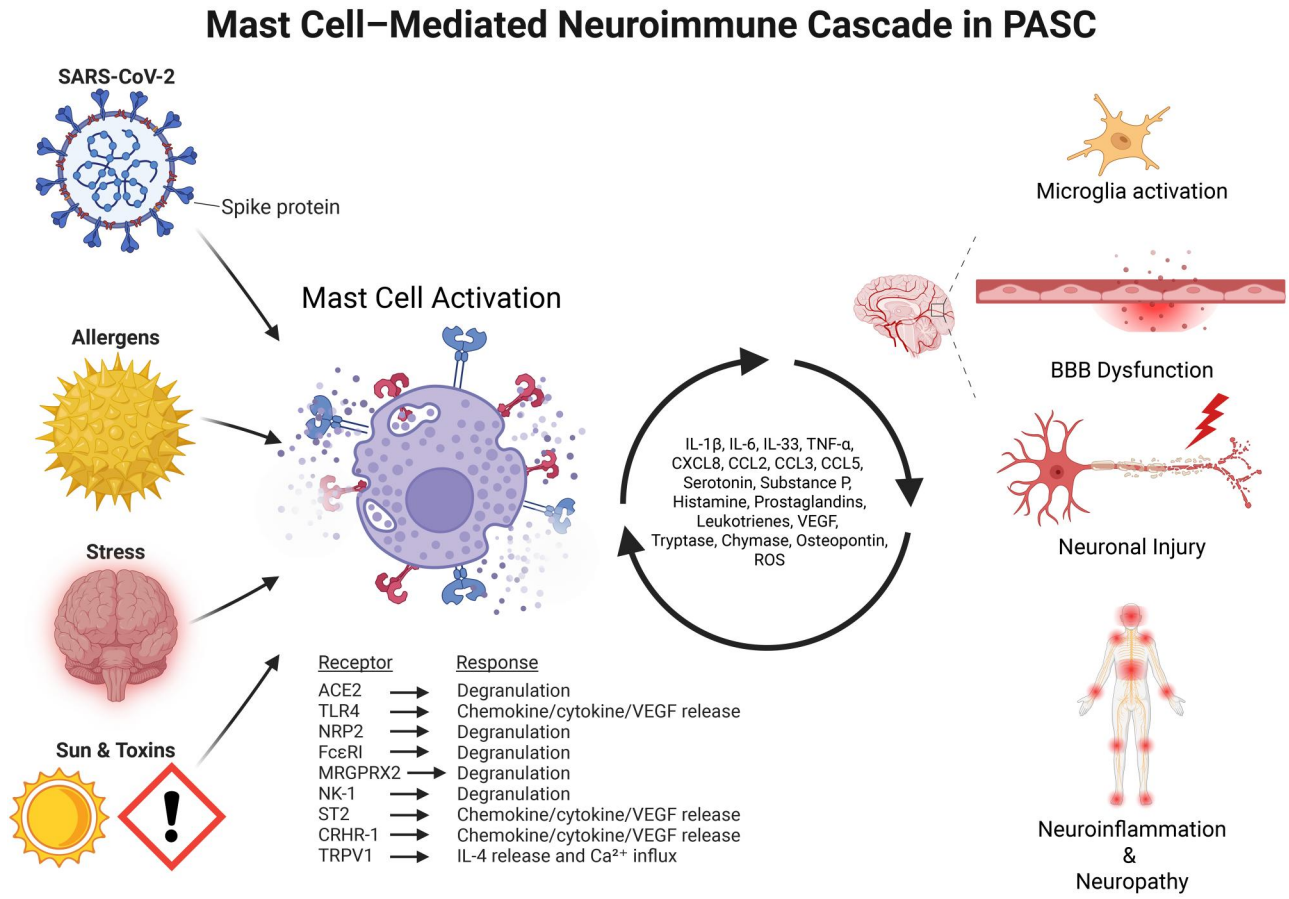


**Figure 2.** Speculative diagrammatic representation of MC-mediated neuroimmune cascade in postacute sequelae of SARS-CoV-2 infection (PASC). SARS-CoV-2 spike protein, and other triggers, such as allergens, stress, ultraviolet radiation, and toxins, activate MCs through interaction with angiotensin-converting enzyme 2 (ACE2), TLR4 receptors, neuropilin-2 (NRP2), FcεRI, Mas-related G protein-coupled receptor X2 (MRGPRX2), neurokinin-1 (NK-1), ST2 (IL-33 receptor), corticotropin-releasing hormone receptor-1 (CRHR-1), and transient receptor potential vanilloid 1 (TRPV1). Activated MCs release pro-inflammatory and neuroactive mediators which sensitize sensory neurons, disrupt the blood-brain barrier (BBB) and activate microglia thereby promoting neuronal injury. This process can result in a feedback loop that sustains MC activation and amplifies injury in the PNS and CNS. This cascade illustrates how persistent MC activation may contribute to the pathophysiology of PASC. Created using BioRender.

this altered spatial distribution may contribute to the development and maintenance of CPRS symptoms.[60]

In traumatic injury, multiple studies found early MC recruitment to lesion sites.[61–64] These MCs degranulate and release potent mediators; including histamine, tryptase, interleukin-6 (IL-6), and tumor necrosis factor alpha; which sensitize nociceptors and amplify neuroinflammation, ultimately exacerbating neural damage. In multiple studies, the influx of MCs and elevated levels of IgE, a potent allergic trigger of MCs, has been associated with the peripheral nerve pathology.[65–68] Another study observed an increase in MC density near injured axons following polyneuropathies of traumatic origin, especially in demyelinating conditions, suggesting the potential role of MCs in demyelinating diseases.[69] In 2 translational studies of postoperative pain, MCs were identified as key sources of pro-inflammatory signaling, including the release of tetrahydrobiopterin and serotonin, at high densities near human sensory nerves. Animal models with MC deletion were protected from the development of neuropathic pain, underscoring the critical role of MCs in mediating pain hypersensitivity in the postoperative setting.[70,71]

Interestingly, a study of rats with traumatic peripheral nerve injury found bone marrow MC transplantation to improve functional recovery and support axonal regeneration.[72] In addition, the stabilization of MCs following traumatic nerve injury in rats did not alter activity or expression of matrix metalloproteinases which are known to be upregulated during inflammatory and degenerative changes.[65,73] This dual role emphasizes the complexity of MC involvement in various neuropathies.

Mast Cells have also been implicated in diabetic neuropathy development. Prior studies describe MC accumulation early on in the progression of diabetic nerves.[74,75] In addition, Batbayar et al. identified increased MC-nerve contacts in diabetic rats.[76] Yao et al. identified dysregulated activation of MCs to release histamine, tryptase, and inflammatory factors into the neural microenvironment and cause neuropathy in diabetic mice.[77] Furthermore, açai berry treatment in diabetic model

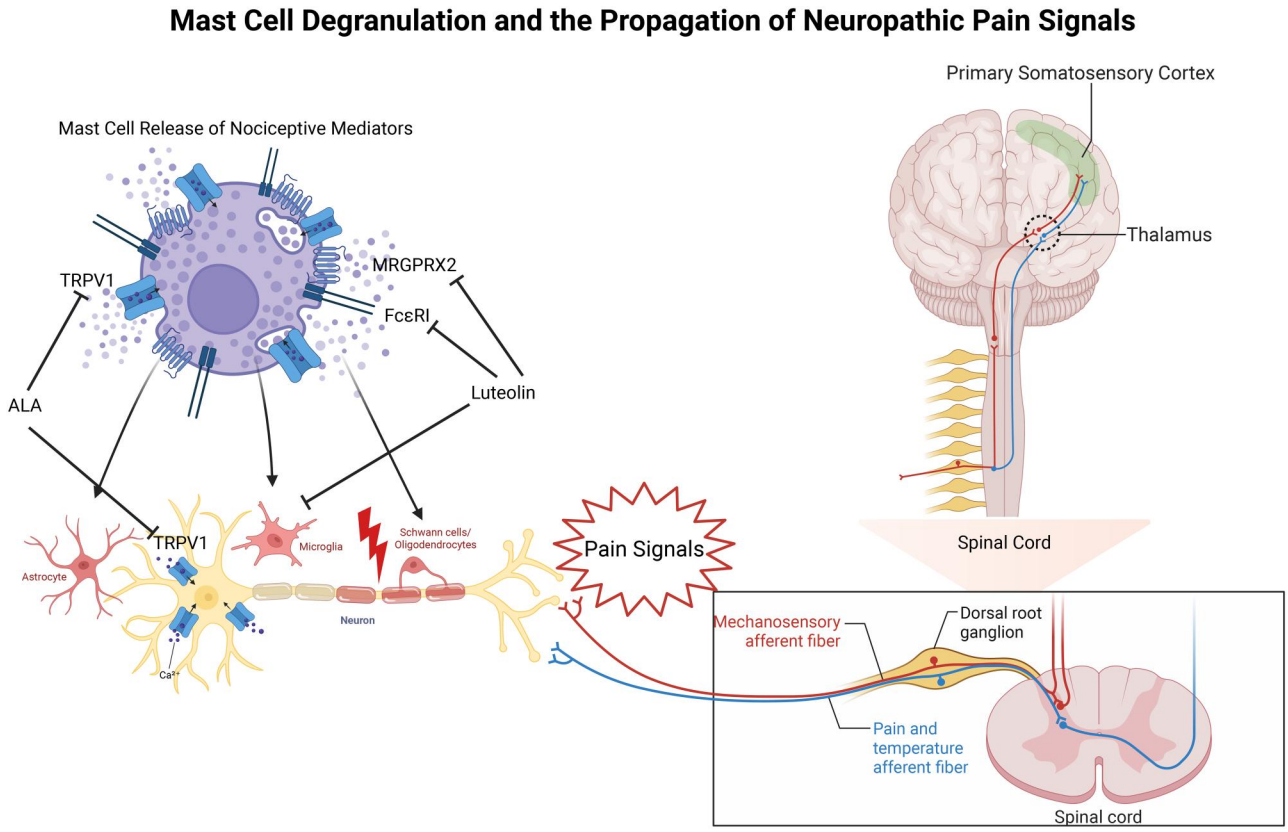


**Figure 3.** Speculative diagrammatic representation of mast cell (MC) degranulation and neuropathic pain signal propagation. This figure illustrates the process of MC degranulation and its role in the propagation of neuropathic pain signals. Upon activation, MCs release inflammatory mediators that exert both direct and indirect neurotoxic effects damaging nearby neurons, Schwann cells in the PNS and oligodendrocytes in the CNS causing demyelination and impaired conduction. These mediators also activate astrocytes and microglia, promoting the release of additional proinflammatory cytokines that amplify neuroinflammation and central sensitization. Likewise, MC-derived mediators such as histamine and prostaglandins sensitize peripheral nociceptors through activation of the transient receptor potential vanilloid 1 (TRPV1) channel, amplifying pain transmission and neurogenic inflammation. This leads to the transmission of pain signals through afferent fibers. The transmission of these signals is depicted as they travel through the dorsal root ganglion and into the spinal cord where they ultimately reach the primary somatosensory cortex and thalamus where pain perception occurs. Alpha-lipoic acid (ALA) may inhibit nociceptive signaling by suppressing TRPV1 activation, while luteolin attenuates MC degranulation by blocking FcεRI and Mas-related G protein-coupled receptor X2 (MRGPRX2) receptor signaling on MCs. Created using BioRender.

mice was found to reduce MC degranulation and ultimately mitigate diabetic neuropathic pain.[78] In a translational study, mice and human models of diabetes found hyperactivity of transient receptor potential vanilloid 1 (TRPV1), which leads to substance P release, triggering MC degranulation. This was found to impair skin perfusion and vascularization and led to progressive diabetic skin neuropathy.[79] Shibata et al. demonstrated in a rat MC-neuron model that 15-deoxy-Δ-prostaglandin $J_2$ (15d-$PGJ_2$), a bioactive MC-metabolite of prostaglandin $D_2$, activates TRPV1 to induce $Ca^{2+}$ influx and enhance neuritogenesis.[80] Another in vitro study reported histamine, an inflammatory mediator of MCs, to enhance the sensitivity of bladder afferents to distension by interacting with histamine H1 receptor and TRPV1. This implicated TRPV1 in bladder hypersensitivity and subsequent pain.[81] Furthermore, TRPV1 is expressed on MCs and activation was found to enhance peripheral inflammatory responses by promoting calcium channel-dependent release of inflammatory mediators, supporting a positive feedback loop.[82,83]

## MCs in PASC

Mast Cells have been proposed as key contributors in PASC or Long COVID syndrome. Multiple preclinical studies report that the SARS-CoV-2 spike protein interacts with cellular receptors and triggers MC activation, ultimately leading to blood-brain barrier (BBB) dysfunction and neuronal injury.[24,56,84] Both the SARS-CoV-2 virus and vaccine spike protein can induce MCAS through similar mechanisms.[85] A case report of a patient with indolent systemic mastocytosis receiving the mRNA-1273 booster demonstrated severe delayed MC activation 24 h postvaccination. This same patient experienced a subsequent MC activation following a later SARS-CoV-2 infection.[86] These parallel vaccine-induced and infection-induced attacks demonstrate that vaccine and viral SARS-CoV-2 spike proteins can trigger MC responses through shared pathways.

In a cross-sectional survey, PASC patients exhibited new-onset symptoms resembling those in MC activation disorders or MC activation syndrome (MCAS) in particular, further

suggesting an association with MC activation in the multisystem symptomatology of PASC.[57] A recent case report proposed MC hyperactivation as a contributing mechanism in PASC patients with comorbid POTS, SFN, and internal tremor symptoms.[87] Another case reported complete remission in a patient with hyperadrenergic POTS and MCAS secondary to PASC after initiating antihistamine therapy.[88] In addition, a study reported that treatment of PASC patients with suspected MC activation with combined fexofenadine (180 mg twice daily) and famotidine (40 mg once daily) resulted in significant improvement in cardiovascular symptoms. Specifically, 29% of patients achieved complete remission, and 85% reported at least partial improvement.[89] Moreover, a case report described improvement in neurocognitive, hypoxic, and microvascular symptomology in a PASC patient treated with H1 and H2 antihistamines (diphenhydramine and famotidine), an MC-stabilizing flavonoid (luteolin), and platelet-activating factor (PAF) antagonism (rupatadine), supporting MCs as a potential contributor to PASC symptomotology.[90] A recent study of 21 patients with severe COVID-19 reported 47.6% (10/21) of patients exhibiting elevated IgE levels with 30 lung autopsies from COVID-19 patients revealing 5-20 CD117+ MCs per high-power field.[91] These findings suggest MC dysfunction can persist beyond acute infection. Furthermore, in a study of 41 patients with PASC osteonecrosis of the femoral head, the key morphological features distinguishing PASC from non-COVID-19 osteonecrosis were clusters of MCs near blood vessels, fibrosis, and arterial and venous thrombi.[92]

While this evidence supports MC activation as a key contributor to the pathogenesis of PASC, a case-control study found no significant differences in the MC activation specific markers, beta-tryptase (TPSB2) and carboxypeptidase (CPA3), suggesting that MC activation may not be a central contributor to the long-term pathogenesis of PASC.[93] However, negative TPSB2 and CPA3 findings do not exclude MC involvement in PASC, as optimal tryptase sample collection is within 30 min to 2 h of symptom onset.[94] In addition, MC activation can be episodic rather than continuous and degranulation can fluctuate with intensity and anatomical location.[95,96] Furthermore, human MCs are capable of releasing up to 390 distinct mediators depending on stimulus and signaling pathway, highlighting a major limitation in relying on single biomarkers like TPSB2 and CPA3.[51,97,98] A summary of the cited literature is provided in Table 1.

## Treatment approaches

While antihistamines may have some benefit, other therapeutic strategies have been explored, including MC stabilizers and flavonoids. Initially, cromolyn sodium was found to inhibit MC degranulation in rat models and gastrointestinal manifestations of systemic mastocytosis; however, subsequent studies have shown cromolyn sodium to be ineffective as a MC inhibitor in both mice and humans.[99–107] Cromolyn sodium shares a similar structure to naturally occurring flavonoids, which are recognized for their anti-inflammatory and antioxidant properties.[108–110] In addition, flavonoids have been shown to influence PAF synthesis.[111] Among flavonoids, quercetin and luteolin were found to suppress allergic activation of cultured human cells.[100,112,113] Luteolin was also found to downregulate brain microglia.[114–117] Compared to cromolyn sodium, luteolin demonstrated superior inhibition of both allergic and nonallergic stimulation of cultured human MCs, and quercetin was more effective in reducing cytokine release from human MCs.[104,118] Luteolin inhibited nuclear factor kappa B signaling preventing release of histamine and IL-31.[112,119] Furthermore, luteolin inhibited activation of the mammalian target of rapamycin in human MCs and inhibited calcium signaling pathways preventing FcεRI- and MRGPRX2-mediated allergic reactions.[112,120] Beyond MC regulation, luteolin exhibits neuroprotective properties, attenuating neuroinflammation and potentially alleviating cognitive dysfunction, particularly brain fog.[121–134] Two dietary supplements formulated in olive pomace oil, 1 containing the natural flavonoids quercetin, and luteolin (FibroProtek) and another containing luteolin, calcium folinate, and hydroxytyrosol (BrainGain), were included in the successful treatment of a patient with PASC.[90]

Alpha-lipoic acid (ALA), or dihydro-lipoic acid, is another naturally occurring compound that serves as a cofactor for mitochondrial alpha-ketoacid dehydrogenase complexes.[135] Alpha-lipoic acid inhibits oxidative stress-inflammation pathways and, in its reduced form dihydrolipoic acid, regenerates oxidized vitamins C and E, chelates transition metals, and modulates signal transduction pathways, including those involved in insulin signaling.[135–137] Furthermore, ALA demonstrates neuroprotective effects and supports nerve regeneration, with clinical studies showing efficacy comparable to standard pharmaceuticals for the treatment of neuropathic pain.[138] Zhang et al. demonstrated that ALA might reduce the effects of TRPV1 by inhibiting NF-κB, thereby alleviating neuropathic pain and reducing the excitability of dorsal root ganglion neurons in diabetes.[139] In addition, Liu et al. reported that suppression of TRPV1 significantly attenuated MC degranulation.[140] Together, flavonoids and ALA target complementary pathways of neuroinflammation and oxidative stress highlighting their potential in treating PASC-associated neuropathy.

## Limitations

The data discussed are still preliminary and lacks generalizability as most studies reporting on MC involvement are based on case reports, case series, or single-center cohorts. The lack of consistent elevation in MC-associated biomarkers suggests that MC involvement in PASC may be heterogeneous or that activation may be predominantly localized rather than systemic, or that it involves additional mediators.[93] In addition, therapeutic responses like those to IVIG appear variable in response effectiveness across patient populations.[89] Therefore, robust, controlled studies are needed to fully elucidate the role of MCs in PASC-related neuropathy and to validate MC-targeted treatments.

# CONCLUSION

This review highlights the plausible involvement of MCs in the development and persistence of neuropathic symptoms

**Table 1.** Literature summary.

| Study | PubMed ID | Type of study | Level of evidence | Sample size ($n$) | Outcome measures | Main findings |
|---|---|---|---|---|---|---|
| Wu et al.[84] | 38638822 | Preclinical | Low | In vivo (mice = 5 each group w/3 control) and in vitro (human brain microvascular endothelial cells and microglia) | Histology, cytokine assays, MC counts in brain vasculature, endothelial barrier integrity | SARS-CoV-2 spike protein induced MCs degranulation, leading to endothelial and microglial inflammation and BBB disruption |
| Zhang et al.[24] | 40304504 | Preclinical | Low | In vitro: human MC line (LAD2) | β-hexosaminidase release, $Ca^{2+}$ flux assays, Src/PI3K/Akt phosphorylation (Western blot), pathway inhibition studies | Coronavirus spike proteins stimulated MC degranulation via Src-PI3K-Akt signaling and $Ca^{2+}$ mobilization |
| Theoharides and Kempuraj[56] | 36899824 | Narrative review | Low | N/A | Histamine, cytokines, BBB permeability (from prior studies) | Synthesizes current literature implicating MC activation in SARS-CoV-2-related neuroinflammation and BBB dysfunction |
| Fajloun et al.[85] | 38693735 | Editorial | Low | N/A | N/A | Proposes that both SARS-CoV-2 infection and vaccinal spike protein can induce MCAS |
| Weiss-Tessbach et al.[86] | 40299000 | Case report; human | Low | 1 | Serum tryptase; plasma histamine; Th2 cytokines (eg, IL-5, IL-6, IL-10); clinical MC activation symptoms | mRNA-1273 booster vaccination induced a delayed, severe MC activation episode with elevated Th2 cytokines; a second MC activation episode occurred during subsequent SARS-CoV-2 infection |
| Weinstock et al.[57] | 34563706 | Cross-sectional survey; human | Moderate | PASC = 136; Control = 136; MCAS = 80 | MC mediator release syndrome (MCMRS) score, fatigue assessments scale (FAS), PASC symptom questionnaire, quality of life | PASC patients had new-onset MCAS-like symptoms similar to MCAS controls after COVID-19 infection |
| Blitshteyn et al.[87] | 39852767 | Case report; human | Low | 1 | Clinical symptoms, autonomic testing, skin biopsy | PASC patient developed SFN, POTS, and internal tremors; symptoms overlapped with MCAS |
| González-Alvarez et al.[88] | 38526146 | Case report; human | Low | 1 | Head-up tilt test (HR/BP response), symptom resolution | Complete remission of hyperadrenergic POTS following H1 antihistamine therapy in a patient with PASC |

(continued)

**Table 1.** (continued)

| Study | PubMed ID | Type of study | Level of evidence | Sample size (*n*) | Outcome measures | Main findings |
|---|---|---|---|---|---|---|
| Salvucci et al.[89] | 37529714 | Retrospective observational treatment study; human | Low-moderate | PASC treated = 14; PASC untreated = 13 | Symptom improvement; physician-assessed HR | H1/H2 blockade treatment associated with symptom improvement in all treated patients, with complete recovery in 29%; no improvement observed in untreated controls |
| Lenning et al.[93] | 39285602 | Case-control lab study; human | Moderate | PASC = 24; Control = 24 | Serum TPSB2 (β-tryptase), CPA3; SF-36 physical functioning | No significant difference in MC markers between PASC and recovered controls |
| Theoharides et al.[90] | 35227867 | Case report; human | Low | 1 | Oxygen requirement, V/Q scan, SPECT imaging, symptoms | Improvement in brain fog, fatigue, and V/Q scan abnormalities after MC-targeted therapy |
| Genova et al.[91] | 41157211 | Retrospective observational clinical and autopsy immunologic study | Low-moderate | 21 patients with acute or postacute COVID-19; lung tissue from 30 COVID-19 autopsies | Serum total IgE; peripheral MC and basophil counts; lung MC and basophil density; cytokine levels (IL-10, IL-33) | Elevated total IgE was observed in 47.6% (10/21) patients, accompanied by reduced circulating MCs and basophils. Analysis of lung tissue from 30 COVID-19 autopsies demonstrated increased pulmonary MC and basophil accumulation with altered cytokine signaling |
| Kuliyeva et al.[92] | 40700078 | Retrospective observational histopathologic study | Low-moderate | PASC ONFH = 41; Non-COVID ONFH = 47 | Histology and morphometry (MC counts, fibrosis area, thrombosed vessels, giant cell granulomas) | Marked MC accumulation and clustering in necrotic bone, fibrotic regions, and perivascular areas, associated with fibrosis and microvascular thrombosis |

Abbreviations: BBB, blood-brain barrier; IL-5, interleukin-5; IL-6, interleukin-6; IL-10, interleukin-10; IL-33, interleukin-33; MC, mast cell; PASC, postacute sequelae of SARS-CoV-2 infection; SNF, small-fiber neuropathy.

associated with PASC. The SARS-CoV-2 spike protein was shown to activate MCs via ACE2 and TLR4, independent of IgE-FcεRI signaling, leading to the release of pro-inflammatory and neurotoxic mediators.[24,56] Beyond ACE2 and TLR4, neuropilins (NRP1 and NRP2) are additional co-receptors for SARS-CoV-2 entry. Neuropilin-2 is strongly expressed on MCs and can bind SARS-CoV-2 spike fragments. Recently, SARS-CoV-2 RNA was detected in neuropilin-positive but ACE2/TMPRSS2-negative MCs in fatal COVID-19 cases, supporting the role of neuropilin-mediated MCs in infection.[141] Mast Cells are strategically located at perivascular, perineural, and epithelial sites in close proximity to the blood vessels and peripheral nerves.[49,61] This location allows for MCs to modulate neurovascular and neuroimmune responses, making these structures vulnerable to injury upon chronic MC activation.[49,57,64] In addition to direct MC activation, SARS-CoV-2 spike protein binding was reported to trigger microglial activation and disrupt the BBB, perpetuating neuroinflammation and ultimately, neuronal damage and degeneration.[56,142] This MC neuroimmune cascade aligns with clinical observations of SFN, autonomic dysfunction, and neuropathic pain in PASC patients. This illustrates the potential of targeted MC interventions to reduce neuroinflammation and neuropathic pain in PASC.

While other hypotheses have been proposed to explain PASC, such as viral persistence, autoimmunity, microclots and endothelial injury, and autonomic deconditioning or central sensitization, these mechanisms are not mutually exclusive.[143] Mast Cell activation intersect with and may amplify these mechanisms. Mast Cell activation potentially can impair viral clearance through MC-mediated immune dysregulation,[144] trigger autoimmune responses through proinflammatory state,[145,146] contribute to endothelial injury and pathologic coagulation through mediator release,[96,147] and directly affect autonomic function due to strategic placement close to blood vessels and peripheral nerves.[49] In addition, the development of MCAS during SARS-CoV-2 infection correlates with PASC development which positions MCs as a potential contributor an integrator of various pathophysiological pathways underlying PASC.[148]

Overall, these findings support the hypothesis that MCs may be key contributors to neuropathic symptoms in PASC. Advancing our understanding in this area will not only contribute to scientific knowledge but, more importantly, will empower physicians to provide more effective care for PASC patients. Postacute sequelae of SARS-CoV-2 infection is a debilitating illness that remains underreported and lacks effective interventions.[2] Clarifying the role of MCs in PASC neuropathy offers a path toward precision treatments that could alleviate suffering and improve quality of life for those affected.

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## CONFLICTS OF INTEREST

T.C.T. is the Scientific Director of Algonot LLC that develops unique dietary supplements.

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