

Neuropsychological Features of Adult Mastocytosis

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KEYWORDS

- Mastocytosis • Mast cell • Kit • Depression • Anxiety • Cognitive impairment
- Headache

KEY POINTS

- Mastocytosis is associated with several and disabling general and neuropsychological symptoms, including pain, headache, anxiety, depression, and cognitive impairment.
- Cognitive impairment in mastocytosis is not linked to depression.
- Anxious and depression symptoms may improve after treatments by tyrosine kinase inhibitors aiming at reducing mast cell activation.

FUTURE CONSIDERATIONS

Neurologic and psychiatric symptoms should be evaluated prospectively on large cohorts of patients. In addition, they should be evaluated in children populations, which are poorly studied in this respect.

New research is needed to better understand the pathophysiology of these manifestations. The results of this research could point out the role of mast cells in neurologic and psychiatric disorders outside mastocytosis.

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INTRODUCTION

Mastocytosis is defined as an excessive accumulation of mast cells in several organs or tissues. In most cases, the disease is indolent and does not reduce life expectancy. The disease is associated, however, with an underestimated chronic disability, presumably linked to the release of mast cell mediators by abnormal mast cells that includes flushes and the well-defined gastrointestinal symptoms, cardiovascular instability, and skin involvement, in particular pruritus and esthetic concerns. In addition, it is well recognized that in almost one-third of the patients, general symptoms, including fatigue and musculoskeletal pain, could also have a major impact on the quality of life. Although less recognized and less attributed to mediators released from abnormal mast cells, symptoms, such as headache, anxiety, mood, and cognitive impairment, are frequent and should be specifically evaluated because they may require specific therapies and are associated with significant impairment of social life and professional activities. In this review, in addition to the authors' studies on psychiatric and neurologic disorders, the major recent findings concerning neuropsychological symptoms in mastocytosis are reviewed and data supporting the hypothesis that abnormal mast cell activation and to a less extent mast cell accumulation are involved in these disorders are discussed.

EPIDEMIOLOGY
Neurologic Features

Few studies are focused on neurologic symptoms associated with mastocytosis (Table 1). In earlier studies of a large cohort of patients, some investigators reported frequent acute or chronic headache; more rarely, syncope and acute-onset back pain; and, in a few cases, clinical and radiological features resembling or allowing a diagnosis of multiple sclerosis.¹⁻³ In addition, several case reports discussed rare associations between mastocytosis and various neurologic conditions, including chorea, encephalopathy, and strokes.⁴⁻⁸ From these studies, it is difficult, however, to link these neurologic manifestations with abnormal mast cell activation and they may have been more fortuitous than causal. Two recent studies, however, reported neurologic symptoms on large cohorts of adult patients with mastocytosis.^{2,3} First, they investigated the occurrence of headache by sending questionnaires to 171 patients with systemic mastocytosis. They received 64 responses, and 36 patients (56.2%) complained of headache.³ These patients displayed headaches, which were classified as migraines (37.5%) or tension-type headaches (17.2%). Second, they tried to identify which complication of the disease could have an impact on the nervous system in a retrospective study of 223 adult patients with mastocytosis.³ The most frequent symptoms they found were headache (n = 78; 35%), followed by syncope (n = 12; 5.4%), acute back

Table 1 Main neuropsychological features in mastocytosis		
Neuropsychological Features	Percentage (%)	Reference
Depression and anxiety	40–60	Moura et al, ²⁵ 2011
Headache	35–56	Smith et al, ³ 2011
Including migraine	37.5	Smith et al, ² 2011
Cognitive impairment	38.6	Moura et al, ³² 2012
Syncope	5	Smith et al, ² 2011
Back pain	4	Smith et al, ² 2011
Multiple sclerosis	1.3	Smith et al, ² 2011

pain ($n = 9$; 4%), and clinical and radiological features, allowing a diagnosis of multiple sclerosis ($n = 3$; 1.3%). The frequency of all these symptoms seems higher than might be expected in the general population of the country in which the study was performed (0.1%), suggesting that mast cell activation may be involved in these disorders.

Depression

In mastocytosis, although mood disorders are clinically observed and are one of the main complaints of patients, specific descriptive literature reports are rare^{9–12} and concern small number of patients. Quantitative and qualitative descriptions of these symptoms in larger cohorts are still missing. In a seminal study by Rogers and colleagues in 1986,⁹ depression frequency and features were investigated. In this study, depression was diagnosed after psychiatric interview in 40% of patients ($n = 10$). In 2008, the authors further reported a prevalence of 75% of depression symptoms among 88 patients with indolent mastocytosis, including cutaneous and systemic forms of the disease.¹³ The authors' first descriptive study looked at a large sample of 288 subjects. The results of this first study showed a prevalence of depression in mastocytosis at approximately 60%, which confirmed the results of previous studies of a smaller number of patients.⁹ The higher prevalence reported in the authors' study could be explained by the different methods of assessment and largely by the choice of a low cut-point of the Hamilton depression rating scale used to consider patients as depressed.

Cognitive Impairment

Soter and colleagues¹² were the first to report cognitive impairment in mastocytosis in the 1970s. In this study, they reported neuropsychiatric symptoms among patients with mastocytosis as "attention and concentration disorders, irritability, fatigue, headache, socio-relational difficulties and poor motivation" in 5 patients of 8.¹² Complaints about memory impairment in mastocytosis have only been specifically studied in 1986 in 10 patients with an old version of the clinical Wechsler Memory Scale.⁹ According to the investigators, most patients presented disorders of cognition affecting memory and attention that fluctuated with the disease and were in some cases improved by histamine antagonists used to control the activity of mast cells. The authors have confirmed these results and shown in 57 patients with mastocytosis that cognitive impairment is a common symptom (38.6%). The prevalence of memory impairment in the authors' sample was high but not as much as suggested by Rogers and colleagues (70% in a sample of 10 patients). In addition, the authors' study provided evidence that memory impairment in mastocytosis was not related to age or level of education of patients (mean age 42 years and high level of education [32%] in the group with disorders). The prevalence of cognitive impairment in the authors' sample was significantly higher than reported in the literature in younger populations (45–59 years) suffering from chronic diseases, such as diabetes, or in the elderly (65 years and over) where the prevalence of cognitive impairment without dementia is approximately 15% to 40%.^{14–17} The prevalence of cognitive impairment in the authors' sample was similar to that observed in multiple sclerosis, an inflammatory disease in which mast cell activation (without mastocytosis) may play a role and in which the prevalence of cognitive impairment is estimated between 40% and 60%.^{18–20}

CLINICAL SYMPTOMS

Neurologic Symptoms

Neurologic symptoms can be acute, related to mast cell mediator release, such as headache and syncope, or permanent, related to mast cell infiltration, such as back

pain, in cases of vertebral infiltration with or without fracture. Headaches were frequently reported in 35% of patients in a large cohort of 223 patients.³ In a second study by the same group based on a smaller number of patients (36 patients) using a questionnaire, it was shown² that 25% of patients displayed chronic daily headache, 37.5% presented migraine, and 17.2% complained of tension-type headache, mostly episodic. Among the patients with migraine, two-thirds reported an associated aura, most frequently visual. Typical aura could be reported with or without migraine among 39% of the patients of the cohort. Symptoms that are clearly associated with abnormal mast cell activity, such as flushes, pruritus, and/or diarrhea, were more common in patients with either tension-type headache or migraine than in patients not reporting headache. Beurey and colleagues²¹ reported syncope as early as in 1971, and this symptom has been more extensively reported by Smith and colleagues³ in 12 patients of 223 with mastocytosis.²² The patients reported by Smith and colleagues had been referred to a neurologist for indeterminate spells with episodic loss of consciousness. When performed, cerebral MRI, electroencephalograms (EEGs), and cardiac evaluations were considered normal. When reported, the spells evolved over the course of several minutes, culminating with a brief syncopal episode. The most commonly associated symptoms were loose stools, abdominal cramps, nausea, hot flushing, light-headedness, palpitations, and diaphoresis, suggesting a role of acute mast cell mediator release. Smith and colleagues³ identified 3 patients with clinical and radiological features compatible with the diagnosis of multiple sclerosis. In this report, 1 man 25 years old and 2 women 57 and 64 years old, respectively, met the revised McDonald clinical criteria for multiple sclerosis. Finally, several case reports were published reporting rare neurologic features associated with mastocytosis, including chorea (n = 2), encephalopathy (n = 2), cerebral infarction (n = 1), coma (n = 1), and strokes with cervical artery dissection (n = 2).^{4-8,23,24} Such isolated case reports may be fortuitous associations and were not confirmed on the large cohort of Smith and colleagues in 2011.

Psychological Symptoms

Depression characteristics and assessment

Although psychological symptoms (depression and disorders of attention and memory) are part of chronic manifestations of mastocytosis, patients suffering from mastocytosis and concerned by these disorders express great suffering linked to the misunderstanding and lack of recognition of their symptoms by themselves but also by physicians or relatives. As discussed previously, no reports in the literature have studied extensively depression characteristics in a large group of patients with mastocytosis. In an attempt to better characterize depression based on a questionnaire, the authors performed, in a large cohort, a detailed analysis of symptoms in patients complaining of mood disorders. The data suggest that depression associated with mastocytosis comprises mainly affective-cognitive aspects (depressed mood, guilt, feelings of failure, and poor motivation [loss of interest in the work and activities]) and anxiosomatic aspects (somatic and psychic anxiety and middle and late insomnia).²⁵ Symptoms like psychomotor slowing and insight problems are rare and are considered atypical symptoms in this population. It is also important to consider the limitation of depression assessment using questionnaires instead of a structured interview diagnosis based on *Diagnostic and Statistical Manual of Mental Disorders* criteria.²⁶ Although the Hamilton Depression Rating Scale is still the gold standard for evaluating depression in clinical trials, it may not be the best choice for mastocytosis patients because of the over-representation of somatic items that may overlap with symptoms of the disease.²⁷⁻²⁹ By studying in detail the Hamilton

score, however, the authors could demonstrate that a high-level score was associated with core depression symptoms, such as sadness and loss of motivation. The use of a more accurate clinical depression scale, the Beck Depression Rating Scale, led to similar results but with a slightly lower rate of depression.^{30,31} The use of more than one scale and/or scales less biased by somatic symptoms should be preferred to screen for depression in mastocytosis. Regardless of the type of questionnaires used, however, it is also important to complete the assessment of patients presenting with more severe symptomatology detected by questionnaires using a psychiatric interview to confirm diagnosis and provide, if necessary, proper medications.

Cognitive impairment characteristics and assessment

Among mastocytosis patients, cognitive symptoms were mostly characterized by attention impairment.^{9,32} Due to their characteristics, cognitive impairment in mastocytosis seems to meet the criteria for an “unspecified cognitive disorder” as described in the *DSM* (Fourth Edition).²⁶ These disorders were not linked to depression, age, level of education, or clinical subcategories. Moreover, no correlation was found between these cognitive disorders and the provision of antihistaminic drugs. In addition to cognitive impairment, lack of motivation is an important symptom to consider in this group of patients. Although difficult to quantify, this symptom shares some links with fatigue and could help understand the primary pathways and mechanisms involved with cognition impairment. Fatigue is a complex symptom composed of both psychic (motivational) and somatic dimensions. The psychic dimension of fatigue is often associated with symptoms, such as pain and affective and cognitive alterations, and is more difficult to characterize.^{33,34} Its behavioral expression (motivation and reward responsiveness), however, has a specific neural circuit involving dopaminergic subcortical structures, such as putamen and anterior cingulate cortex, that could be implicated in difficulties to sustain attention and/or to engage in even simple actions among these patients.³⁵ Assessment of cognitive impairment in mastocytosis should be more systematic in patients with complaints and should focus on attention and auditory memory and executive functions as well.

PATHOPHYSIOLOGY

Although the pathophysiology of infiltrative complications, such as spinal cord compression, is easy to understand by a mechanical role of mast cell infiltration of vertebral bone, the pathophysiology of fatigue, cognitive dysfunction, psychiatric symptoms, and headache remains unclear (**Fig. 1**).

Mast Cells in the Brain

Mast cells are present in variable quantities in all tissues and organs, especially along vessels, including the brain, which is rich in mast cells. In this organ, they are preferentially located near blood vessels at the level of the blood-brain barrier and also at the nerve endings of sensory and sympathetic fibers.³⁶ In addition, mast cells are found particularly and in high density in certain structures of the diencephalon, especially in the hypothalamus, which is involved in systems of stress response, emotion, and cognition, and also in amygdalae, in the ventral portion of the median eminence, near the pituitary gland at these anterior and posterior sides as well as in the hippocampal formation and surrounding leptomeninges and meningeal spaces at the level of the olfactory bulb.^{37–43} A large number of mast cells reside in the thalamus, which lesions or stimulation of the dorsomedial portion and earlier kernels have been associated with changes in emotional reactivity and pain.^{38,44–47}

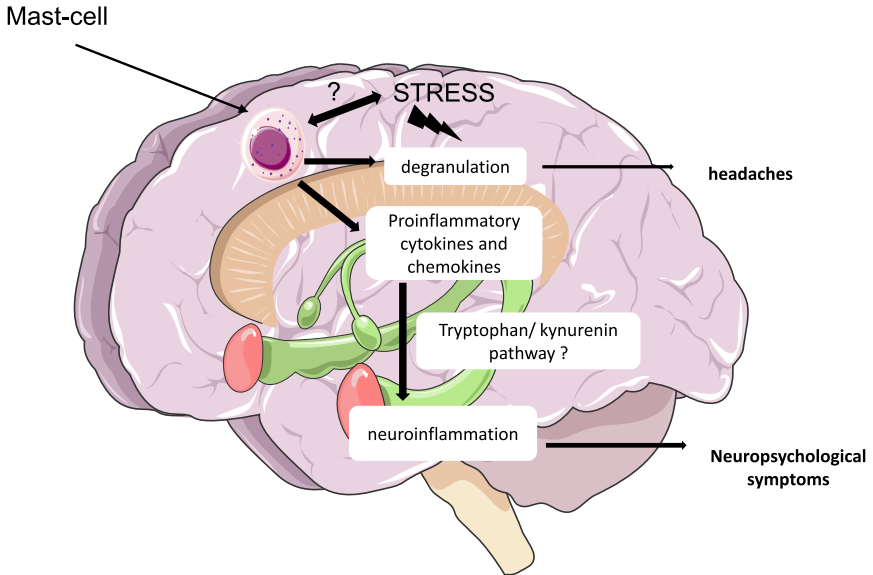


Fig. 1. How mast-cells might be involved in the etiology of neuropsychiatric symptoms associated to mastocytosis? (Adapted from Selvier Medical Art.)

Mast Cells, Stress Response, Cognition, and Emotionality

Because of their particular distribution and density in related brain structures, mast cells' overactivity may interfere with brain function and adversely affect stress response, cognition, and emotionality.^{37,42,48–57} In a previous work, the authors showed that patients with mastocytosis displayed high levels of perceived stress linked to lower telomere length.³¹ Perceived stress results from cognitive and emotional evaluation of situations by individuals. The brain structures involved in physiological stress response are also implicated in cognitive appraisal as well as emotion and behavioural responses to adversity. In mastocytosis, in line with other studies in the field of stress, chronic hyperactivation of the stress response system has been hypothesized to explain the high prevalence of neuropsychological symptoms as well as a high tendency to perceive stress in conventional situations.^{31,58–61} The pathologic variation of the number and the activation of mast cells in the brain could lead to a dysfunction of these systems. In line with these observations, negative emotion expressed in mastocytosis could also result from conditioning process involving responses to stress. Mast cells could be recruited through aversive conditioning. Once conditioning is obtained, psychological cues could lead to mast cell activation,^{62–64} which could maintain aberrant responses to stress.

Mast Cell Neuroinflammation and Depression

The cytoplasm of mast cells contains many granulations of preformed mediators, such as histamine, tryptase, serotonin, cytokines, and chemokines (interleukin [IL]-3, IL-4, IL-5, IL-6, IL-8, granulocyte macrophage–colony-stimulating factor, and TNF- α),^{23,30,31} which, in cases of abnormal release, may explain part of all the symptoms found in patients with mastocytosis, including olfactory hypersensitivity, headache and migraines, pain, and probably mood, anxiety, and cognitive disorders. Histamine has a modulator effect in some mnemonic systems, but its exact function in memory remains controversial.^{65–67} In their study of memory disorders in

mastocytosis, Roger and colleagues⁹ suggested that histamine might be responsible for memory disorders in mastocytosis. Their hypothesis was based on the fact that their patients improved their neuropsychiatric symptomatology with antihistamine drugs. Serotonin produced by mast cells contributes to hippocampal function.⁶⁸ In mastocytosis, Kushnir-Sukhov and colleagues^{69,70} have shown that patients displaying gastrointestinal and neuropsychological symptoms presented low levels of serum serotonin. In line with these studies, it could be hypothesized that an abnormal deviation of the metabolism of the serotonin produced by mast cells may interfere with normal function of the hippocampus and may be involved in the memory loss observed in patients with mastocytosis. In addition, it is not excluded that inflammatory mast cell cytokines, like $\text{TNF-}\alpha$, could also trigger depression in mastocytosis.^{56,71–76} Several studies have shown that inflammation related to mediator release by mast cells is linked to depression.^{34,73,77–84} Moreover, inflammation could lead to activation of indoleamine 2,3-dioxygenase (IDO), which breaks down tryptophan into kynurenine, explaining fatigue^{35,85} and cognitive impairment⁸⁶ through accumulation of kynurenic acid and quinolinic acid and possibly the reduced levels of serotonin in mastocytosis patients.⁷⁰

Mast Cells and Headache

In migraine, mast cells might be involved through their interactions with peptidergic and cholinergic neurons.⁸⁷ At this level, presynaptic endings may capture mediator release by mast cell granules.^{44,88–90} In agreement with this hypothesis, some studies have suggested a direct role of mast cell degranulation in headache⁹¹ and found that symptoms reflective of mast cell activity were significantly greater in individuals reporting headaches.² Vascular instability in periphery may result in poor perfusion of the brain but could also be related to prostaglandin and histamine release at the brain level.³

Mast Cells and Multiple Sclerosis

The role of mast cells in the pathophysiology of multiple sclerosis is extensively suggested in the literature. Mast cells are detected in human multiple sclerosis lesions and increase mast cell activity, as assessed by a high level of tryptase, is detectable in the cerebrospinal fluid of patients with active multiple sclerosis.^{92–95} Furthermore, several studies have found an association between mast cell burden and susceptibility to experimental autoimmune encephalitis.^{3,96}

DIAGNOSIS

Neuropsychiatric symptoms are thus frequently associated with mastocytosis and may present as various clinical features. Clinicians may face 2 situations.

Mastocytosis Was Not Previously Diagnosed

In patients with cognitive and/or mood complaints in which mastocytosis was not previously diagnosed, associated clinical symptoms and signs in favor of this diagnosis should be looked for. In the presence of skin lesions, the diagnosis of mastocytosis is easy and a usual clinical investigation should be made that may include skin biopsies, bone marrow aspiration and biopsy, and measurement of tryptase levels. Tryptase levels and eventually bone marrow aspiration and biopsies should be performed in cases of the presence of unusual psychiatric features or symptoms compatible with mast cell activation, including mainly gastrointestinal symptoms, flushes, pruritus, bone and musculoskeletal pains, and osteoporosis. In these cases,

a diagnosis of mastocytosis could be made following the standard World Health Organization criteria but in some cases no evidence of mast infiltration may be found and the diagnosis of mast cell activation syndrome could be proposed. Mast cell activation syndrome has recently been described and diagnostic criteria have been written and include patients presenting with symptoms suggesting mast cell degranulation without any diagnostic criteria for a specific entity.⁹⁷ The absence of a clonal mast cell population suggests that in this entity, mast cells are quantitatively normal but qualitatively abnormal, probably with a lower threshold of activation. Some studies suggest that this not well-defined entity is genetically determined. Overall, stabilizing mast cells or inhibiting effects of mast cell degranulation with therapeutics, such as antihistamine or cromolyn sodium, is effective for some symptoms, such as pruritus or GI tract disturbances, but, except for a few case reports,⁹ their impact on psychiatric symptoms is not known.

Mastocytosis Was Previously Diagnosed

When a diagnosis of mastocytosis is already known, because of their high frequency, neuropsychiatric symptoms should be systematically investigated. Unfortunately, both by patients and physicians, they are still not linked to mastocytosis in a significant number of cases. When confronted with neurologic and psychiatric symptoms, specialists in neurology and psychiatry should perform a specific and extensive work-up. Then, in some cases, more specific examinations should be performed, including cerebral scan or MRI. In cases of neurologic deficits and/or headaches, cardiac testing with ECG and Holter ECG rule out cardiac rhythm dysfunction; neurologic assessment with EEG to eliminate seizure in case of syncope should be performed. Acute back pain should prompt neuroimaging of the spine to look for vertebral fracture with the risk of spinal cord compression. If a diagnosis of multiple sclerosis is suspected, cerebrospinal MRI and lumbar puncture should be performed.

TREATMENT

Treatment of indolent mastocytosis aims to relieve symptoms and requires a therapeutic adjustment tailored to each patient profile. Therefore, the treatment is essentially symptomatic.⁹⁸ Until recently, the treatment was intended mainly to prevent and limit degranulation and/or its consequences. Only in aggressive forms does the treatment aim to control the proliferation of tumor mast cells. New therapeutic approaches are being developed, including tyrosine kinase inhibitors, aimed at blocking the tyrosine kinase activity of KIT or other kinases involved in mast cell activation, like Lyn. Aspirin has been thought efficacious in the prophylaxis against syncope in mastocytosis.¹

Psychotherapeutic Interventions

Although depression symptoms in mastocytosis seem related to systemic aspects of the disease, the implication of mast cells in stress response, behavior, and emotion regulation has been suggested by several studies.⁶⁸ Health psychology focuses on the impact of physical illness on emotions and cognitions. The concept of *emotional adjustment* is often used to understand how an individual negotiates emotionally with the impact of physical illness and its symptoms. In this process of psychological adaptation to the disease, patients may develop specific cognitions that reflect the way they build their understanding of what is happening to them. The concept of “sense of coherence,” developed by Antonovsky in the 1970s, describes an understanding of events by individuals (sense of comprehensibility), feeling that they can

manage (sense of manageability) and feeling they have a sense (sense of meaningfulness). The sense of coherence promotes better emotional adjustment to disease.^{99–103} Therefore, a cognitive-behavioral approach with pragmatic strategies and information to improve understanding of the disease and the development of personal emotional management strategies of certain symptoms may be of greater benefit to these patients than psychodynamic approaches. Besides this general approach to psychological consequences of the disease, methods focusing on emotion and stress management, such as mindfulness meditation,¹⁰⁴ could also promote better cognitive and psychological adjustment. They might even contribute to interrupting the stress–mast cell activation interplay by reducing both psychological stress as a mast cell activation promoter and biologic stress as a mast cell activation consequence.

Psychotropic Drugs

According to general guidelines,¹⁰⁵ patients with a formal diagnosis of moderate to severe depression should benefit from an antidepressant prescription with well-tolerated antidepressants, such as selective serotonin reuptake inhibitors (SSRIs). Moreover, it has been shown that SSRIs can reduce endotoxin-induced fatigue¹⁰⁶ and even prevent depression induced by high-dose interferon-alpha, another condition related to inflammation.¹⁰⁷ Considering noradrenaline and dopamine involvement in motivation and lack of energy,^{108,109} other classes of antidepressants, such as monoamine oxidase inhibitors, the noradrenaline and dopamine reuptake inhibitor bupropion, and serotonin-norepinephrine reuptake inhibitors or tricyclics, could also be prescribed. In another condition with debilitating fatigue, multiple sclerosis (MS), amantadine has shown efficacy in approximately one-third of patients.¹¹⁰ The wake-promoting agent modafinil could also be prescribed if required. Alternatively, antidepressants with hypnotic properties, such as mianserin or mirtazapine, alone or in association, could target insomnia and decrease central histamine effects. Finally, in line with anti-histamine drugs use, further studies could assess the benefits of blockade of mediators released by mast cells. Neurokinine-1 antagonists, such as aprepitant, showed promise in animal studies and early clinical trials as novel antidepressants.¹¹¹ Even if larger clinical trials did not confirm this property, aprepitant might target cognitive impairment and/or depression in mastocytosis or in patients with mast cell activation. Similarly, the tumor necrosis factor antagonist infliximab has been recently shown to improve depressive symptoms in patients with high baseline inflammatory biomarkers¹¹² and could target fatigue⁷⁸ in other conditions. Finally, ketamine or other *N*-methyl-D-aspartate (NMDA) receptors antagonists, such as memantine, might be useful to treat depression¹¹³ and fatigue through blockade of NMDA stimulation by quinolinic acid after IDO activity increase.⁸⁵

Tyrosine Kinase Inhibitor Therapy

KIT (CD117) is the receptor for the stem cell factor that is the main cytokine involved in mastocytogenesis. Adult patients with systemic mastocytosis usually have mutations in *c-Kit* (D816V), which allows abnormal survival, proliferation, and activation of these cells.⁹⁸ The only kinase inhibitor that has been investigated for the effect of mast cell inhibition on neuropsychiatric symptoms is masitinib. Masitinib is an oral inhibitor selectively blocking c-Kit wild-type, platelet-derived growth factor receptor, and Lyn kinase activities. When tested in vivo in symptomatic patients with systemic mastocytosis, masitinib was able to decrease clinical symptoms linked to the release of mast cell mediators.¹³ Among these symptoms, psychiatric symptoms, including depression, cognitive impairment, and anxiety, were significantly improved. The authors

showed, in a sample of 35 patients, that masitinib treatment was associated (50%–67% of cases) with a significant improvement in depression (independently), with 25% to 75% remission, depending on the criteria chosen for depression. Treatment with masitinib was associated with a significant reduction of the scores of the dimension involving the mental depression symptoms, such as depressive mood anxiety and guilt. This result suggests that the improvement of depression may be influenced by the inhibitory effect of masitinib on the activation of mast cells and is consistent with the probable systemic nature of depression in this disease. Although these results do not definitively demonstrate the role of mast cells in the depression in mastocytosis, it highlights their probable contribution.

SUMMARY

Neuropsychological symptoms in mastocytosis are not rare. Neurologic features are dominated by headache but various neurologic symptoms can occur. Urticaria pigmentosa and unexplained recurrent episodes of flushing, palpitations, abdominal pain, and loss of consciousness with spontaneous recovery may alert a neurologist to a possible systemic mastocytosis diagnosis. Depression and cognitive impairment (attention and memory) are 2 common symptoms in mastocytosis that are not linked causally. Patients with mastocytosis have increased sensitivity to stress that has been associated with peripheral leukocyte shorter telomeres³¹ and may participate in diseases associated with mastocytosis. Further work is warranted to assess whether or not cardiovascular diseases, cancer, and aging are more frequent in mastocytosis than in other systemic diseases. Alternatively, mast cells could be the link between reactive stress and anxiety and shortening telomere.¹¹⁴ This hypersensitivity to stress could suggest a hyperactivation of the response to stress through the mast cells in this pathology. This hyperactivation could be linked to the high prevalence of depression among these patients. Finally, if the entanglement of biologic and psychological factors in this disease seems important, the role of emotional regulation mechanisms, including difficulties in identifying emotions in the holding of depressive symptomatology, is not excluded, and this aspect of the emotional functioning of these patients can be an attractive therapeutic target for those with more severe depressive symptomatology. In addition, drugs that specifically inhibit release of mast cells and/or that reduce their number may be attractive to improve these symptoms and in extension could be useful in some psychiatric and neurologic disorders, as recently suggested with kinase inhibitors in multiple sclerosis¹¹⁵ and Alzheimer disease.⁷¹

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