



Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases



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ABSTRACT

Neurologists and psychiatrists frequently encounter patients whose central and/or peripheral neurologic and/or psychiatric symptoms (NPS) are accompanied by other symptoms for which investigation finds no unifying cause and for which empiric therapy often provides little to no benefit. Systemic mast cell activation disease (MCAD) has rarely been considered in the differential diagnosis in such situations. Traditionally, MCAD has been considered as just one rare (neoplastic) disease, mastocytosis, generally focusing on the mast cell (MC) mediators tryptase and histamine and the suggestive, blatant symptoms of flushing and anaphylaxis. Recently another form of MCAD, MC activation syndrome (MC), has been recognized, featuring inappropriate MC activation with little to no neoplasia and likely much more heterogeneously clonal and far more prevalent than mastocytosis. There also has developed greater appreciation for the truly very large menagerie of MC mediators and their complex patterns of release, engendering complex, nebulous presentations of chronic and acute illness best characterized as multisystem polymorbidity of generally inflammatory ± allergic themes – including very wide arrays of central and peripheral NPS. Significantly helpful treatment – including for neuropsychiatric issues – usually can be identified once MCAD is accurately diagnosed. We describe MCAD's pathogenesis, presentation (focusing on NPS), and therapy, especially vis-à-vis neuropsychotropes. Since MCAD patients often present NPS, neurologists and psychiatrists have the opportunity, in recognizing the diagnostic possibility of MCAD, to short-circuit the often decades-long delay in establishing the correct diagnosis required to identify optimal therapy.

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1. Introduction

In clinical practice neurologists and psychiatrists frequently encounter patients whose central and/or peripheral neurologic and/or psychiatric symptoms (NPS) are accompanied, persistently or episodically, by a variety of other multi-system symptoms for which investigation often finds no cause and for which empiric therapy often provides little to no benefit. Systemic mast cell

activation disease (MCAD) has rarely been considered in the differential diagnosis in such situations. Traditionally, MCAD has been considered as just allergic phenomena together with rare, neoplastic mastocytosis in assorted forms. Furthermore, although mast cell (MC) activation is widely appreciated to cause readily clinically appreciable flushing and anaphylaxis, little is known about the vast array of mediators released by activated MCs and their necessarily vast array of clinical consequences. Thus, the rarity of mastocytosis and absence (in mysteriously multisystemically unwell neuropsychiatric patients) of the “textbook classic” symptoms of MC activation conspire to deter physicians from considering MCAD in their diagnostic thinking. Here we review the currently known spectrum

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of MC activation symptoms and the recently recognized form of MCAD known as mast cell activation syndrome (MCAS) whose prevalence and clinical behavior now make MCAD, and particularly MCAS, a reasonable differential diagnostic consideration in many patients – and all the more important to recognize given that effective therapy can be found for most MCAD patients. We will describe the manifestations of MCAD (with a focus in the central and peripheral nervous systems) as well as pathogenetic and therapeutic issues (especially vis-à-vis neuropsychotropic drugs used in MCAD patients).

2. Mast cells: Basic biology

Originating in hematopoietic tissue (and with reservoirs of precursors in white adipose tissue, too, [Poglio et al., 2010](#)) MCs are immune cells that secrete pre-stored mediators, such as histamine and tryptase, as well as numerous *de novo* synthesized chemokines and cytokines in response to allergic or non-immune triggers. MCs act as effector immune cells and as regulatory immune cells and play central roles in adaptive and innate immunity ([Gri et al., 2012](#)). This versatility is reflected in numerous activation stimuli with intracellular pathways that intersect to modulate the quality and magnitude of the MC response. The best characterized mechanism of MC activation is cross-linking of IgE bound to FcεRI on mast cells by antigen contact. In addition, human MCs express a multiplicity of G-protein-coupled receptors and other recognition sites on their surface which are IgE-independently involved in MC activation under physiological and pathophysiological conditions.

Apart from being prominently involved in allergic reactions, MCs are critical for development and maintenance of integrity and function in all tissues, thus explaining their ubiquitous, if typically sparse, presence in all tissues. Their central role in

immunological as well as non-immunological processes is further reflected by the large number of mediators (>200) by which MCs may influence other cells ([Lundequist and Pejler, 2011; Ibelgaufits, 2015](#)). The profile of mediators and cytokines stored or produced *de novo* in MCs can markedly differ between and even within organs/tissues depending upon a wide array of macro- and micro-environmental factors including antigenic and physical stimuli. Their mediators allow MCs to regulate local tissue functions and host defense by acting as innate immune cells, by interacting with the specific immune system, and by inducing and regulating inflammation. Since MCs tend to site themselves at the body's environmental interfaces, they are perfectly equipped with their mediators to significantly participate in orchestration of the immune system. They can recruit other immune cells to the site of injury and control the function of various cells such as other granulocytes and T and B lymphocytes, thereby acting to protect the organism against bacterial, parasitic and viral infections. MC actions can be targeted very precisely because, apart from their ability to release pre-stored mediators via classic non-selective whole-MC degranulation (as in anaphylaxis), MCs also can selectively release specific patterns of mediators by morphologically distinct secretory pathways referred to as piecemeal or differential degranulation ([Theoharides et al., 2007, e1, e2, e3, e4](#)). In addition, MCs are essential to the regulation of homeostasis. In this respect, they contribute to wound healing as well as tissue remodeling, e.g., in hair follicles and bones ([Ng, 2010, e5, e6, e7](#)). MCs also promote homeostasis by degrading, via their potent proteases, certain endogenous toxins such as endothelin-1 or neurotensin released in response to bacterial infection and bacterial toxins. It is understandable, then, that the very same mechanisms that enable MCs to protect the organism can wreak focused or multisystem havoc when uncontrolled.

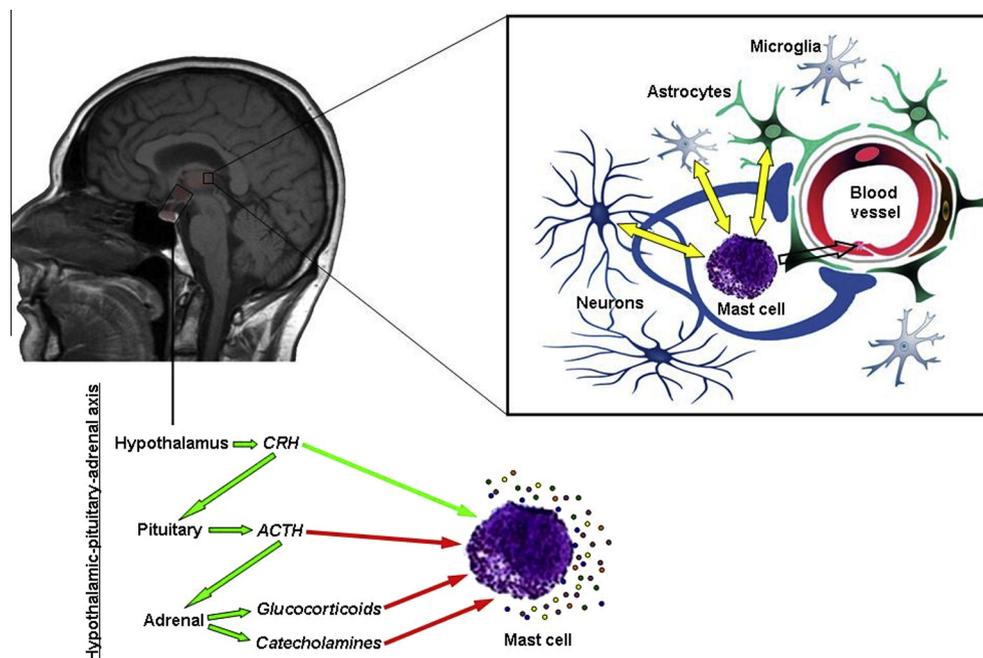


Fig. 1. Mast cell siting in the CNS. The highest densities of mast cells (MCs) in brain are found in the infundibulum, pituitary gland, area postrema, choroid plexus, hypothalamus, and thalamus (shaded red in the MRI picture). Emotional, physical, or inflammatory stress triggers corticotropin releasing hormone (CRH) secretion from the hypothalamus, in turn activating CRH receptors on MCs in the diencephalon and possibly also in the periphery. MC-derived neurosensitizing, proinflammatory, and vasoactive mediators can then induce central nervous symptoms in MCAD. In addition, the hypothalamic–pituitary–adrenal axis is activated, influencing the activation of MCs in the periphery (red arrows: inhibitory effects; green arrows: activating effects). Bidirectional interactions between MCs, microglia, astrocytes, and neurons in the central nervous system are depicted in the box. Upon stimulation MCs can release vasodilatory and inflammatory mediators (e.g., histamine, interleukin-6, vascular endothelial growth factor, tumor necrosis factor- α). As a result of dysregulation of this network by inappropriately activated MCs, neuroinflammation is induced. Histamine and proteases effect leakage of the blood–brain barrier at the tight junctions (black arrow), resulting in infiltration of circulating lymphocytes and also MCs by diapedesis. Focal brain inflammation can contribute to brain dysfunction, e.g., seizures, autistic behavior, hallucination, etc.

3. Physiological and pathophysiological roles of mast cells in brain

MCs have been detected in the brains of all vertebrates so studied thus far, certainly including the human brain (Khalil et al., 2007, e8, e9). Reliable information about the absolute number of MCs in the brain are lacking. The highest densities of MCs in brain have been found in the infundibulum, pituitary gland, area postrema, choroid plexus and in the region around the 3rd ventricle of cerebrum, the hypothalamus and thalamus (Fig. 1) (Porzionato et al., 2004; Turygin et al., 2005; Maślińska et al., 2005). The phenotype of any given MC is determined by its local environment. For example, MCs in the hypothalamus lack tyrosine kinase KIT (i.e., the receptor for stem cell factor SCF) (Pang et al., 1996; Shanas et al., 1998), and thalamic MCs do not express cyclooxygenase (Dubayle et al., 2005), thus precluding direct susceptibility to treatments aimed at these targets when the MCs become pathologically activated. Since MCs are located on the brain side of the blood–brain barrier as well as in the leptomeninges, they can communicate with neurons, glia cells, microglia and vascular endothelial cells by releasing their mediators or by direct physical contact (Fig. 1) (Kovacs et al., 2006; Ito et al., 2008). MC mediators are differentially released under normal conditions (i.e., not by total degranulation as in an anaphylactic reaction) and can spread through brain tissue volume several orders of magnitude greater than a synaptic cleft (Nautiyal et al., 2009).

Ninety percent of thalamic histamine and up to 50% of total brain histamine is synthesized by MCs in those sites (Goldschmidt et al., 1985). Histamine is one of the most important neurotransmitters in brain, activating H₁ and H₃ histamine receptors to help drive a variety of biological functions such as thermoregulation, regulation of food intake, cerebral seizures, arousal, anxiety, reward and memory (Zarrindast et al., 2008; Dere et al., 2010; Gianlorenço et al., 2012). Hence, MCs in brain and other tissues can influence brain functions directly by releasing histamine.

It is well known that stress can modulate the function of the immune system. The neuropeptide corticotropin-releasing hormone (CRH) is in the vanguard of the hypothalamic–pituitary–adrenal axis (Fig. 1). Stress induces the release of CRH from hypothalamic neurons, thereby stimulating secretion of adrenocorticotropic hormone from the pituitary gland into blood circulation, driving synthesis and release of the stress hormone cortisol. In addition, CRH as well as the neuropeptide neurotensin are able to distinctly trigger MC activation by a nuclear factor κ B-dependent mechanism to the point of degranulation (Alysandratos et al., 2012, e10, e11, e12). Other neuropeptides such as substance P (SP) and vasoactive intestinal polypeptide (VIP) have been demonstrated to activate MCs by engaging specific receptors in the MC membrane (Kulka et al., 2008).

In addition to neuronally mediated activation of MCs, MCs in turn, through their mediators and cytokines, can activate neurons, eliciting emotional, cognitive, and sensorimotor changes and disturbances (Reichenberg et al., 2001; McAfoose and Baune, 2009). It has been confirmed in a large number of animal experiments that MCs can modulate behaviors (Silver and Curley, 2013, e13, e14). Since the MC-induced changes in behavior are probably the result of a shift in the balance of a variety of neurotransmitters in the CNS, a simple linear correlation between MC density, mediator release, and behavior is not to be expected.

Several studies related to the role of the brain hormone melatonin in the functioning of MCs have been published. Both resting and stimulated RBL-2H3 cells (a rat MC line) synthesized and released melatonin (Maldonado et al., 2010). The necessary enzymatic machinery for the synthesis of melatonin has been shown

to be present in MCs, and it also has been shown that these cells express both the MT1 and MT2 melatonin membrane receptors (Maldonado et al., 2010). Based on these results, it has been suggested that melatonin probably has a regulatory effect on inflammatory reactions mediated by MCs (Maldonado et al., 2010). It has been observed that melatonin is released by MCs in the late phase of secretion and that melatonin inhibits the activation of MCs, probably by an autocrine mechanism (Calvo et al., 2013).

MCs are versatile gatekeepers of pain (Chatterjea and Martinov, 2015). Both CNS-localized and peripheral nervous system (PNS)-localized MCs are involved in the pathogenesis of neuroinflammation and in the development and maintenance of neuropathic pain (Nelissen et al., 2013; Demir et al., 2013, e15, e16, e17). MCs residing in close proximity to unmyelinated nerve fibers, such as the nociceptive C-fibers (as has been shown in inflammatory bowel syndrome Levy et al., 2012, irritable bowel syndrome Barbara et al., 2006, and vulvodynia Bornstein et al., 2008), can undergo ultrastructural alterations that spur differential mediator release (Lavich et al., 2003). Adhesion molecules such as N-cadherin and cell adhesion molecule-1 (CADM-1) facilitate MC-nerve junctions (e18). MC-derived nerve growth factor (NGF) has been shown to lower the threshold of nociceptor firing through its binding to a potassium transporter TRK1-transforming tyrosine kinase (trkA) (e19, e20). Another important signal at the MC-nerve synapse is substance P. Released by both neurons and MCs, SP leads to production of prostaglandins, leukotrienes, tumor necrosis factor- α , and interleukin-6 by MCs (Kawabata, 2011; Okuse, 2007). Binding of SP to MC-surface neurokinin-1 receptors primes MCs to degranulate upon repeated application of lower doses of substance P (Janiszewski et al., 1994).

Taken together, the broad spectrum of functions of MCs might explain why dysfunctional MCs seem to be pathologically involved in so many different neurological and psychiatric disorders (Table 1).

4. Systemic mast cell activation disease

Systemic mast cell activation disease (MCAD) denotes a group of primary polygenic MC disorders (Molderings, 2015) characterized not only by aberrant release of variable subsets of MC mediators but also sometimes by generally anti-apoptotic accumulation of such dysfunctional MCs in potentially any or all organs and tissues (Molderings et al., 2011). Due to both the widespread distribution of MCs and the great heterogeneity of aberrant mediator expression patterns, symptoms can occur in virtually all organs and tissues; hence, the clinical presentation of MCAD is very diverse, sometimes to the even-further-confounding point of presenting polar opposite abnormalities in different patients. According to current proposed classifications of MCAD (Molderings et al., 2011; Valent et al., 2012), the traditionally recognized rare variant termed systemic mastocytosis (SM) is characterized by a specific pattern of neoplastic MC proliferation and associated somatic mutations in exon 17 of the tyrosine kinase KIT (for which K1173E accounts for the great majority (Haenisch et al., 2012) together with certain immunohistochemical and serologic findings (known as the World Health Organization (WHO) criteria Valent et al., 2001, 2007) also associated with these mutations. SM is further divided into several subtypes. The other principal type of MCAD, only recently recognized, is termed mast cell activation syndrome (MCAS). Like SM, MCAS is seemingly born of sets of mutations in various genes (including all domains of KIT Molderings et al., 2007, 2010) and presents a complex clinical picture of multiple MC-mediator-induced symptoms, but unlike SM, the mutations in MCAS seem to drive relatively little MC

Table 1

Neurological and psychiatric diseases for which pathogenetic involvement of mast cells has been demonstrated in humans and/or animal models.

- Autism (own observation and e46, e47, e48, e49).
- Fibromyalgia (own observation and Lucas et al., 2006, e24).
- Migraine (e48, e50, e51, e52).
- Neuropathic pain (own observation and Demir et al., 2013, e17, e53, e54).
- Complex regional pain syndrome (previous synonyms: Morbus Sudeck, Sudeck-dystrophia, Algodystrophia) (e55, e56).
- Multiple sclerosis (Nelissen et al., 2013; Smith et al., 2011).
- Alzheimer's disease (Nelissen et al., 2013).
- Parkinsonism (e57).
- Neurofibromatosis (e58, e59).
- Vulvodynia (own observation and Bornstein et al., 2008).

accumulation, and MCAS patients fail to meet the WHO criteria for diagnosis of SM (Molderings et al., 2011; Valent et al., 2012, e21, e22). Importantly for the clinician (and the patient), though MCAS may lack hallmark histologic and biochemical features of SM (e.g., marked proliferation, aggregation and spindling of MCs, and tryptase overexpression), these two major types of MCAD have largely equivalent potentials for wreaking multisystem havoc via aberrant mediator production and release.

As first studied in Germany, the corrected prevalence for MCAD may be as high as 5–10% of the general population (Molderings et al., 2013). This high prevalence should not be surprising since MCAS may be an underlying cause of various common idiopathic chronic inflammatory entities, e.g., fibromyalgia (Lucas et al., 2006, e23, e24) and irritable bowel syndrome (Frieling et al., 2011, e25, e26). Confirmation will be required, of course, but this finding suggests that MCAS may be a common disorder, in contrast to SM, whose prevalence is a rare 1 in 364,000 (Haenisch et al., 2012).

The high prevalence of MCAD implies that some neurologists and/or psychiatrists, like many other physicians, may treat MCAD patients without recognition of that diagnosis and with the possible consequence of misinterpreting the NPS of MCAD (Table 2) as independent neurological or psychological disorders. Unawareness of MCAD and its prevalence also often leads to erroneous assessment of MCAD symptoms as psychosomatic complaints or as a somatoform disorder.

4.1. How to diagnose mast cell activation disease

On the basis of enormous growth in knowledge of MC (patho-)physiology in the last decade, largely similar proposals for diagnostic criteria for, and treatment of, MCAD have been published by multiple expert groups, as synopsized in eTable 2 (Molderings et al., 2011; Valent et al., 2012, e21, e27, e28, e29).

MCAD is first suspected on clinical grounds, typically based on recognition of symptoms potentially referable to MC mediator release and, in some, identification of typical rashes and skin lesions. The clinical presentation of MCAD is very diverse, since due to both the widespread distribution of MCs and the great heterogeneity of aberrant mediator expression patterns, symptoms can occur in virtually all tissues and systems (Table 2 and eTable 1) (Afrin et al., 2013). Moreover, symptoms often occur in a temporally staggered fashion, waxing and waning over years to decades. Over time, symptom-free intervals tend to shorten, and finally symptoms become chronic with intensity which fluctuates but with an overall trend toward steadily increasing intensity. Especially in MCAS, symptoms often initially manifest during adolescence or even childhood or infancy but usually are non-specific and recognized only in retrospect as MCAD-related. An approach to the diagnostic work-up is shown in Fig. 2 (Afrin and Molderings, 2014). Determination of levels of relatively specific MC mediators in blood and urine (eTable 2), and detection (in some patients) of

increased MC density in tissue samples (typically from the gastrointestinal tract or bone marrow), are central to the diagnostic process (eTable 2). Diagnosis and classification of MCAD can then be achieved by the criteria listed in eTable 2.

5. Neurological and psychiatric aspects of MCAD

5.1. Neurological and psychiatric symptoms of MCAD

In studies over the last decade, at least 40–60% of MCAD patients exhibited NPS (Table 2) (Hermine et al., 2008; Smith et al., 2011, e30, e31, e32, e33, e34, e35), whereas the prevalence of NPS in the general population is below 10% (e30). The exact mechanisms that underlie NPS in MCAD are not yet understood in detail, but causal involvement of acute or chronic excessive MC activation seems certain (Fig. 1) (Kushnir-Sukhov et al., 2008, e36, e37). In the majority of cases of MCAD, there seems to be initially an activation of peripheral MCs, i.e., MCs located outside the CNS. Irrespective of the origin of this MC activation, mediators are transported by the bloodstream to the brain, where their effects are integrated with MC-mediator-related changes in neural afferents from the periphery. The resulting neuronal reactions and adjustments clinically manifest in personality and behavior changes, cognitive dysfunction, and central and peripheral nervous symptoms. There are no systematic studies about the exact incidence of MCAD primarily localized in the central nervous system (CNS); hence, further studies (e.g., comparison of MC mediator levels in the periphery vs. CNS in situations of acute and chronic excessive MC activation) are necessary.

Given the ready effects of MCAD on the CNS and PNS, drug therapy aimed at the reduction of MC activation often leads to an improvements in NPS (Ashina and Ashina, 2004, e30 and authors' observation). Also of note, peripheral blood levels of certain neuropeptides (CRH, SP, somatostatin, VIP, calcitonin gene-related peptide) and expression of corresponding receptors are increased in the MCs in MCAD patients. Thus, a synergistic activating effect of neuropeptides on MCs can be assumed (Maintz et al., 2011; Peng et al., 2013, e12). Furthermore, when one considers the triggering of pathologically hyperexcitable MCs by neuropeptides CRH and neurotensin (Alysandratos et al., 2012, e10, e11), it becomes likely that the intensity of MCAD symptoms is regularly modulated by psychologically stressful situations (whether positive or negative in nature) and that physicians not experienced with MCAD can misinterpret MCAD symptoms as somatization. In this context, it is important to know that there is no correlation between the intensity of NPS in MCAD and the intensity of other symptoms in MCAD (Hermine et al., 2008, e37 and authors' observations).

Neuropathic pain in MCAD is an especially vexing symptom for both patient and physician, as such pain frequently changes in intensity and localization due to its MC genesis. Sometimes, a simple initial attempt at treatment in the form of omission of gluten and cow's milk protein from the diet can prove effective (e38,

Table 2
Neurologic and psychiatric symptoms and findings in MCAD (all symptoms listed were also observed by the authors).

Specialty	Possible symptoms of MCAD
Neurology	<ul style="list-style-type: none"> • Headaches (in particular migraine-like) (Silver and Curley, 2013; Afrin et al., 2013; Afrin and Molderings, 2014; Hermine et al., 2008; Smith et al., 2011; Ashina and Ashina, 2004, e36, e48, e51, e52, e60), • presyncope and/or syncope (Afrin et al., 2013; Afrin and Molderings, 2014; Smith et al., 2011), • peripheral (usually) distal sensory and/or motor neuropathy and paresthesia (Afrin et al., 2013; Hermine et al., 2008, e15, e61, e60), • intradural adhesions in some circumstances with compression of the spinal cord (eFig. 1) (e62), • syrinx-like findings in the spinal cord (eFig. 2), • chronic inflammatory demyelinating polyneuropathy (Afrin et al., 2013; Smith et al., 2011), • mixed organic brain syndrome (Hermine et al., 2008, e32), • mast cell mediator-induced hypoxia/ischemia with resulting symptoms (e.g., parkinsonism, encephalopathy) (Silver and Curley, 2013, e15, e63, e33, e57), • Parkinsonism (e63), • hemorrhage due to MCAD-induced bleeding and cerebral venous thrombosis with resulting symptoms (e34, e35, e64, e65), • unclear medullary lesions on MRI (e33; own observations), • transient chorea (e66, e67), • tics (Afrin et al., 2013; Afrin and Molderings, 2014), • tremor (typically resting tremor) (Afrin et al., 2013; Afrin and Molderings, 2014), • restless-leg-like symptoms (own observations), • abnormal electroencephalography, epileptiform disorders (often resistant to treatment) (e68, Afrin et al., 2013, e70, e71; own observations), • sleep disorder (different forms) (Afrin et al., 2013, e30, e36), • irresistible drowsiness/sleep attacks (e36, e60), • acoustic startle (e14), • selective hyperacusis (often bass response) (Afrin and Molderings, 2014), • tinnitus (Hermine et al., 2008), • neuronal symptoms of allergy (e74), • pain hypersensitivity (e75).
Psychiatry	<ul style="list-style-type: none"> • Gratuitous upset (e.g., angry, depressed) (Hermine et al., 2008, e32), • motivation disorder (Hermine et al., 2008, e30, e37, e69), • depressive episode (Hermine et al., 2008, e30, e32, e37, e70, e60), • bipolar affective disorder (Afrin et al., 2013; Afrin and Molderings, 2014), • attention deficit hyperactivity disorder (Afrin et al., 2013; Afrin and Molderings, 2014), • anxiety disorder (e30, e14, e72, e60), • posttraumatic stress syndrome (Afrin et al., 2013; Afrin and Molderings, 2014), • visual hallucinations that disappear under blockade of mast cells (own observations), • panic attacks (Afrin et al., 2013), • hyperventilation tetany-like symptoms (Afrin and Molderings, 2014), • psychosis (e73), • disturbance of memory (Afrin et al., 2013; Hermine et al., 2008, e31, e32, e70), • word-finding difficulties (Afrin et al., 2013, e32), • difficulties in concentrating (Hermine et al., 2008, e31, e32, e70, e69).

e39), perhaps because unregulated increased MC activation may induce non-IgE-mediated hypersensitivity to these dietary substances and perhaps also because these food substances are known to non-specifically stimulate the intestinal immune system and thereby activate intestinal mucosal MCs. In this context, it should be borne in mind that a non-celiac gluten sensitivity may be the reason for the clinical picture of gluten ataxia, believed to account for about 20% of all progressive ataxia and 45% of idiopathic sporadic ataxias (e38, e40). Strikingly successful pharmacotherapy of neuropathic pain in MCAD patients can be achieved with benzodiazepines, cannabinoids, and the IgE antibody omalizumab (Molderings et al., 2011; Hugel et al., 2003; Grotenhermen and Müller-Vahl, 2012). In experimental use an improvement of neuropathic pain was achieved with certain tetracyclines such as minocycline (independent of its antibiotic properties) (e41, e42, e43).

5.2. Limitations in the use of neuropsychotropic drugs in MCAD patients

The complex network of different pathomechanisms of MCAD symptoms (release of a variety of mediators; stimulation of MC activation and mediator release by a variety of neurotransmitters and stimuli; influencing of other immune cells such as T and B lymphocytes with resulting development of allergic and non-allergic hypersensitivity including intolerances) regularly leads to hypersensitivity of MCAD patients to a variety of xenobiotics, including neuropsychotropic drugs (Table 3).

Generally, neuroleptics, antidepressants and monoamine oxidase inhibitors appear to inhibit the release of mediators from MCs in low (ordinarily therapeutically irrelevant) concentrations, and to induce mediator release at high (therapeutically relevant) concentrations (Church and Graddidge, 1980). Representatives of these medication classes for which a predominantly inhibitory effect was observed on MCs are listed in Table 3. Due to their mechanism of action, reuptake inhibitors of neurotransmitters induce an increase in transmitter concentration in the vicinity of the MCs, which thereby can be activated via the corresponding excitatory receptors. Patients often report a worsening of MCAD symptoms after initiation of selective serotonin reuptake inhibitors (SSRIs), but positive effects of such drugs on MCAD have been observed, too (own observations, LBA). Since there are no predictive biomarkers for positive or negative effects of reuptake inhibitors in MCAD patients, such drugs (particularly SSRIs) should be used with reservation and caution in MCAD patients. Because most benzodiazepines bind with high affinity to a recently discovered recognition site on activated MCs (e44, e45), they accumulate in the brain only slowly and in small concentrations, and thus high doses often are required when using such drugs to treat brain illness such as epilepsy. Exceptions in this respect are clonazepam and triazolam, which bind little to MC-surface benzodiazepine recognition sites and therefore are suitable for anticonvulsant therapy or treatment of insomnia (Table 3). Finally, it should be noted that regardless of research findings on the tolerability of drugs in MCAD, each drug can induce intolerance symptoms in the individual MCAD patient. Of note, MCAD patients commonly are

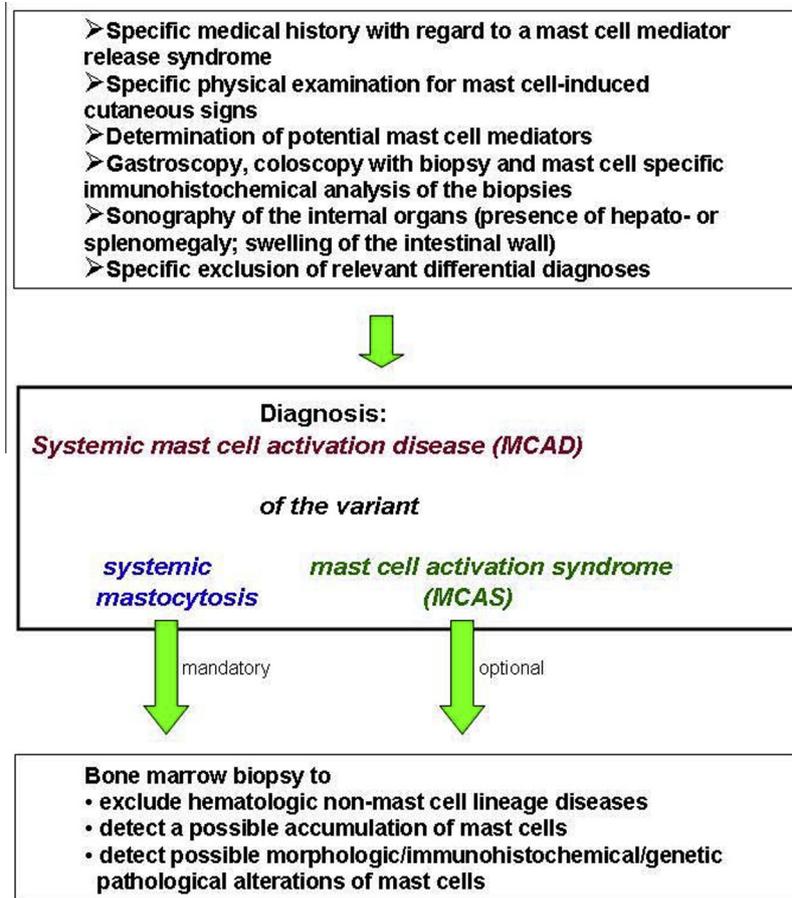


Fig. 2. Diagnostic algorithm when a systemic mast cell activation disease (MCAD) is suspected.

Table 3

Neuropsychiatric disorder drug therapies which may trigger mast cell mediator release. Compilation of drugs for the treatment of central nervous system and peripheral nervous disorders that are associated with a high risk of release of mediators from MCs and their therapeutic alternatives in MCAD patients.

Medical indication	Substance group	Drugs with proven or theoretically high risk of mast cell activation	Drugs with a low, absent, or inhibitory effect on mast cells
Psychopharmacological therapy	Neuroleptics		Clozapine (e77, e78), chlorpromazine (e81), haloperidol (e78) Amitriptyline (e76, e88, e89), doxepin (e88), clomipramine (e88, e89), imipramine (e88), maprotiline (e89)
	Antidepressants		
	Selective dopamine- and norepinephrine reuptake inhibitors	Bupropion (e87)	
	Selective serotonin – reuptake inhibitors	All (often poorly tolerated dependent on individual factors) (e60, own unpublished experiences)	
Anticonvulsive therapy		Carbamazepine (e86), topiramate (own unpublished experiences)	Clonazepam, diazepam (e90)
Treatment of Parkinson's disease			Dopamine receptor agonists (e79); clozapine (e77, e78), bromocriptine (e78)
Analgesics	Opioid analgesics	Meperidine, morphine, codeine (e90, e91, e92, e93)	Remifentanyl, alfentanil, fentanyl, piritramide, oxycodone (e90, e91, e93, e94)
	Peripheral acting analgesics	All non-steroidal anti-inflammatory drugs (NSAIDs), if symptoms of intolerance have occurred in the health history (e60, e95)	Paracetamol, metamizole (e90, e93, e94) etoricoxib (own unpublished experiences) other: palmitoylethanolamide (e82, e84) cannabinoids (Grotenhermen and Müller-Vahl, 2012, e80, e85)
	Local anesthetics	Ester-type: tetracaine procaine (e90)	Amide-type: bupivacaine (e94)
Therapy of neuropathic pain			Abstention of gluten and cow's milk protein (e96) benzodiazepines (flunitrazepam, lorazepam) (own unpublished experiences) palmitoylethanolamide (e82, e84) cannabinoids (Grotenhermen and Müller-Vahl, 2012, e80, e85) omalizumab (own unpublished experiences) minocycline (tetracyclines) (e41, e83)
Sleep disorders			Triazolam (own unpublished experiences)

intolerant of various drugs because of reactivities directed against excipients (e.g., fillers, binders, dyes, preservatives) rather than active ingredients, and thus sometimes trials of alternative formulations of a quickly, or unusually, offending drug can identify not only a tolerable formulation but also reveal the identities of specific offending excipients, with such information then helping to guide global medication management in the patient.

5.3. Role of psychotherapeutic techniques in the treatment of MCAD

Although NPS in MCAD reflect systemic dissemination of MC disease, individual patient circumstances may still permit psychotherapy co-treatment to be helpful. Psychotherapy may be necessary to support patients in mentally coping with the incurability of the disease, and psychotherapy also can illustrate strategies for dealing with the social environment that often reacts uncomprehendingly and adversely against the MCAD patient. To this end, cognitive-behavioral methods may be more useful than psychodynamic approaches. Finally, activation of MCs by psychological stress (e.g., via CRF [Alysandratos et al., 2012](#)) may be lessened by psychotherapeutic treatment which successfully reduces stress.

6. Conclusions

When NPS are associated with chronic or recurrent multisystem disturbances of otherwise unclear unifying origin, systemic MCAD should be included early in the differential diagnosis. The presence of MCAD can be suspected clinically on the basis of mediator-induced symptoms after exclusion of relevant differential diagnoses (e.g., carcinoid, pheochromocytoma, primary cardiac dysrhythmias, porphyria). In principle, MCAD therapy consists of attempts to reduce pathologically increased MC activation and to ameliorate consequences of inappropriate release of MC mediators. In MCAD patients, NPS and other symptoms often improve with specific MCAD therapy targeted at MC mediator production and action. Pharmacotherapy of MCAD can be supported by cognitive-behavioral psychotherapeutic techniques in selected cases. Physicians should be aware of challenges in use of various classes of neuropsychotropic drugs.

Contributions

Dr. Molderings conceived the project. Drs. Afrin, Molderings, and Raithel drafted the paper. All authors contributed to editing and approved the final version.

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Disclaimer statement

All authors report no conflicts of interest.

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Dr. Molderings conceived the project. Drs. Afrin, Molderings, and Raithel drafted the paper. All authors contributed to editing and approved the final version. No funding or other support was received for this work from any source. All authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bbi.2015.07.002>.

References

- Afrin, L.B., Molderings, G.J., 2014. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J. Hematol.* 3 (1) 1–17. <http://dx.doi.org/10.5315/wjvh.v3.i1.1>. Available at: <<http://www.wjnet.com/2218-6204/pdf/v3/i1/1.pdf>>.
- Afrin, L., 2013. Presentation, diagnosis, and management of mast cell activation syndrome. In: *Mast Cells: Phenotypic Features, Biological Functions, and Role in Immunity*. Nova Science Publishers, Hapauge, NY, pp. 155–231. Available at: <https://www.novapublishers.com/catalog/product_info.php?products_id=42603> (accessed 14.06.15).
- Alysandratos, K.D., Asadi, S., Angelidou, A., Zhang, B., Sismanopoulos, N., Yang, H., Critchfield, A., Theoharides, T.C., 2012. Neurotensin and CRH interactions augment human mast cell activation. *PLoS One* 7, e48934. <http://dx.doi.org/10.1371/journal.pone.0048934> (PMID: 23155429).
- Ashina, S., Ashina, M., 2004. Headache in systemic mastocytosis: a case report with pathophysiological considerations. *Cephalalgia* 25, 314–316. <http://dx.doi.org/10.1111/j.1468-2982.2004.00852.x> (PMID: 15773831).
- Barbara, G., Stanghellini, V., De Giorgio, R., Corinaldesi, R., 2006. Functional gastrointestinal disorders and mast cells: implications for therapy. *Neurogastroenterol. Motil.* 18, 6–17. <http://dx.doi.org/10.1111/j.1365-2982.2005.00685.x> (PMID: 16371078).
- Bornstein, J., Cohen, Y., Zarfati, D., Sela, S., Ophir, E., 2008. Involvement of heparanase in the pathogenesis of localized vulvodynia. *Int. J. Gynecol. Pathol.* 27, 136–141. <http://dx.doi.org/10.1097/pgp.0b013e318140021b> (PMID: 18156988).
- Calvo, J.R., González-Yanes, C., Maldonado, M.D., 2013. The role of melatonin in the cells of the innate immunity: a review. *J. Pineal Res.* 55, 103–120. <http://dx.doi.org/10.1111/jpi.12075> (PMID: 23889107).
- Chatterjea, D., Martinov, T., 2015. Mast cells: versatile gatekeepers of pain. *Mol. Immunol.* 63, 38–44. <http://dx.doi.org/10.1016/j.molimm.2014.03.001> (PMID: 24666768).
- Church, M.K., Gradidge, C.F., 1980. Inhibition of histamine release from human lung in vitro by antihistamines and related drugs. *Br. J. Pharmacol.* 69, 663–667 (PMID: 23008748).
- Demir, I.E., Schorn, S., Schremmer-Danninger, E., Wang, K., Kehl, T., Giese, N.A., Algül, H., Friess, H., Ceyhan, G.O., 2013. Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. *PLoS One* 8, e60529. <http://dx.doi.org/10.1371/journal.pone.0060529> (PMID: 23555989).
- Dere, E., Zlomuzica, A., De Souza-Silva, M.A., Ruocco, L.A., Sadile, A.G., Huston, J.P., 2010. Neuronal histamine and the interplay of memory, reinforcement and emotions. *Behav. Brain Res.* 215, 209–220. <http://dx.doi.org/10.1016/j.bbr.2009.12.045> (PMID: 20060425).
- Dubayle, D., Malissin, I., Menétrey, D., 2005. Differential effects of two analgesic drugs, morphine chlorhydrate and acetylsalicylic acid, on thalamic mast cell numbers in rat. *J. Neuroimmunol.* 169, 106–115. <http://dx.doi.org/10.1016/j.jneuroim.2005.08.008> (PMID: 16169091).
- Frieling, T., Meis, K., Kolck, U.W., Homann, J., Hülsdonk, A., Haars, U., Hertfelder, H.J., Oldenburg, J., Seidel, H., Molderings, G.J., 2011. Evidence for mast cell activation in patients with therapy-resistant irritable bowel syndrome. *Z. Gastroenterol.* 49, 191–194. <http://dx.doi.org/10.1055/s-0029-1245707> (PMID: 21298604).
- Gianlorenço, A.C., Serafim, K.R., Canto-de-Souza, A., Mattioli, R., 2012. Emotional memory consolidation impairment induced by histamine is mediated by H1 but not H2 receptors. *Brain Res. Bull.* 89, 197–202. <http://dx.doi.org/10.1016/j.brainresbull.2012.09.003> (PMID: 22986235).
- Goldschmidt, R.C., Hough, L.B., Glick, S.D., 1985. Rat brain mast cells: contribution to brain histamine levels. *J. Neurochem.* 44, 1943–1947 (PMID: 3989570).
- Gri, G., Frossi, B., D'Inca, F., Danelli, L., Betto, E., Mion, F., Sibillano, R., Pucillo, C., 2012. Mast cell: an emerging partner in immune interaction. *Front. Immunol.* 3, 120. <http://dx.doi.org/10.3389/fimmu.2012.00120> (PMID: 22654879).
- Grotenhermen, F., Müller-Vahl, K., 2012. The therapeutic potential of cannabis and cannabinoids. *Dtsch. Arztebl. Int.* 109, 495–501. <http://dx.doi.org/10.3238/arztebl.2012.0495>.
- Haenisch, B., Nöthen, M.M., Molderings, G.J., 2012. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. *Immunology* 137, 197–205. <http://dx.doi.org/10.1111/j.1365-2567.2012.03627.x> (PMID: 22957768).
- Hermine, O., Lortholary, O., Leventhal, P.S., Catteau, A., Soppelsa, F., Baude, C., Cohen-Akenine, A., Palmérini, F., Hanssens, K., Yang, Y., Sobol, H., Fraytag, S., Ghez, D., Suarez, F., Barete, S., Casassus, P., Sans, B., Arock, M., Kinet, J.P., Dubreuil, P., Moussy, A., 2008. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One* 3, e2266. <http://dx.doi.org/10.1371/journal.pone.0002266> (PMID: 18509466).
- Hugel, H., Ellershaw, J.E., Dickman, A., 2003. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. *J. Pain Symptom Manage.* 26, 1073–1074. <http://dx.doi.org/10.1016/j.jpainsymman.2003.09.005> (PMID: 14654258).
- Ibelgafts, H., 2015. Mast cells. In: *COPE: Cytokines and Cells Online Pathfinder Encyclopaedia*. Available at: <<http://www.copewithcytokines.de/cope.cgi?key=mast%20cells>> (accessed 4.02.15).

- Ito, A., Hagiyama, M., Oonuma, J., 2008. Nerve-mast cell and smooth muscle-mast cell interaction mediated by cell adhesion molecule-1, CADM1. *J. Smooth Muscle Res.* 44, 83–93. <http://dx.doi.org/10.1540/jmsr.44.83> (PMID: 18552455).
- Janiszewski, J., Bienenstock, J., Blennerhassett, M.G., 1994. Picomolar doses of substance P trigger electrical responses in mast cells without degranulation. *Am. J. Physiol.* 267, C138–C145 (PMID: 7519394).
- Kawabata, A., 2011. Prostaglandin E2 and pain – an update. *Biol. Pharm. Bull.* 34, 1170–1173. <http://dx.doi.org/10.1248/bpb.34.1170> (PMID: 21804201).
- Khalil, M., Ronda, J., Weintraub, M., Jain, K., Silver, R., Silverman, A.J., 2007. Brain mast cell relationship to neurovasculature during development. *Brain Res.* 1171, 18–29. <http://dx.doi.org/10.1016/j.brainres.2007.07.034> (PMID: 17764664).
- Kovacs, P., Hernadi, I., Wilhelm, M., 2006. Mast cells modulate maintained neuronal activity in the thalamus in vivo. *J. Neuroimmunol.* 171, 1–7. <http://dx.doi.org/10.1016/j.jneuroim.2005.07.026> (PMID: 16300831).
- Kulka, M., Sheen, C.H., Tancowny, B.P., Grammer, L.C., Schleimer, R.P., 2008. Neuropeptides activate human mast cell degranulation and chemokine production. *Immunology* 123, 398–410. <http://dx.doi.org/10.1111/j.1365-2567.2007.02705.x> (PMID: 17922833).
- Kushnir-Sukhov, N.M., Brittain, E., Scott, L., Metcalfe, D.D., 2008. Clinical correlates of blood serotonin levels in patients with mastocytosis. *Eur. J. Clin. Invest.* 38, 953–958. <http://dx.doi.org/10.1111/j.1365-2362.2008.02047.x> (PMID: 19021721).
- Lavich, T.R., Cordeiro, R.S., Calixto, J.B., e Silva, P.M., Martins, M.A., 2003. Combined action of vasoactive amines and bradykinin mediates allergen-evoked thermal hyperalgesia in rats. *Eur. J. Pharmacol.* 462, 185–192. [http://dx.doi.org/10.1016/S0014-2999\(02\)02947-3](http://dx.doi.org/10.1016/S0014-2999(02)02947-3) (PMID: 12591112).
- Levy, D., Kainz, V., Burstein, R., Strassman, A.M., 2012. Mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. *Brain Behav. Immun.* 26, 311–317. <http://dx.doi.org/10.1016/j.bbi.2011.09.016> (PMID: 22019552).
- Lucas, H.J., Brauch, C.M., Settas, L., Theoharides, T.C., 2006. Fibromyalgia – new concepts of pathogenesis and treatment. *Int. J. Immunopathol. Pharmacol.* 19, 5–9 (PMID: 16569342).
- Lundequist, A., Pejler, G., 2011. Biological implications of preformed mast cell mediators. *Cell Mol Life Sci.* 68, 965–975. <http://dx.doi.org/10.1007/s00018-010-0587-0> (PMID: 21069421).
- Maintz, L., Wardelmann, E., Walgenbach, K., Fimmers, R., Bieber, T., Raap, U., Novak, N., 2011. Neuropeptide blood levels correlate with mast cell load in patients with mastocytosis. *Allergy* 66, 862–869. <http://dx.doi.org/10.1111/j.1398-9995.2011.02550.x> (PMID: 21284654).
- Maldonado, M.D., Mora-Santos, M., Najji, L., Carrascosa-Salmoral, M.P., Naranjo, M.C., Calvo, J.R., 2010. Evidence of melatonin synthesis and release by mast cells. Possible modulatory role on inflammation. *Pharmacol. Res.* 62, 282–287. <http://dx.doi.org/10.1016/j.phrs.2009.11.014> (PMID: 19963060).
- Maślińska, D., Laure-Kamionowska, M., Gujski, M., Czurzynska, G., Wojtecka-Lukasik, E., 2005. Post-infectious distribution and phenotype of mast cells penetrating human brains. *Inflamm. Res.* 54 (Suppl. 1), S15–S16. <http://dx.doi.org/10.1007/s00011-004-0406-x> (PMID: 15928815).
- McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. *Neurosci. Biobehav. Rev.* 33, 355–366. <http://dx.doi.org/10.1016/j.neubiorev.2008.10.005> (PMID: 18996146).
- Molderings, G.J., 2015. The genetic basis of mast cell activation disease – looking through a glass darkly. *Crit. Rev. Oncol. Hematol.* 93, 75–89. <http://dx.doi.org/10.1016/j.critrevonc.2014.09.001> (PMID: 25305106).
- Molderings, G.J., Kolck, U.W., Scheurlen, C., Brüß, M., Homann, J., Von Kügelgen, I., 2007. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand. J. Gastroenterol.* 42, 1045–1053. <http://dx.doi.org/10.1080/00365520701245744> (PMID: 17710669).
- Molderings, G.J., Meis, K., Kolck, U.W., Homann, J., Frieling, T., 2010. Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 62, 721–727. <http://dx.doi.org/10.1007/s00251-010-0474-8> (PMID: 20838788).
- Molderings, G.J., Brettner, S., Homann, J., Afrin, L.B., 2011. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J. Hematol. Oncol.* 4, 10. <http://dx.doi.org/10.1186/1756-8722-4-10> (PMID: 21418662).
- Molderings, G.J., Raithe, M., Kratz, F., Azemar, M., Haenisch, B., Harzer, S., Homann, J., 2011. Omalizumab treatment of systemic mast cell activation disease: experiences from four cases. *Intern. Med.* 50, 611–615. <http://dx.doi.org/10.2169/intermalmedicine.50.4640> (PMID: 21422688).
- Molderings, G.J., Haenisch, B., Bogdanow, M., Fimmers, R., Nöthen, M.M., 2013. Familial occurrence of systemic mast cell activation disease. *PLoS One* 8, e76241. <http://dx.doi.org/10.1371/journal.pone.0076241> (PMID: 24098785).
- Nautiyal, K.M., McKellar, H., Silverman, A.J., Silver, R., 2009. Mast cells are necessary for the hypothermic response to LPS-induced sepsis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296, R595–R602. <http://dx.doi.org/10.1152/ajpregu.90888.2008> (PMID: 19109365).
- Nelissen, S., Lemmens, E., Geurts, N., Kramer, P., Maurer, M., Hendriks, J., Hendrix, S., 2013. The role of mast cells in neuroinflammation. *Acta Neuropathol.* 125, 637–650. <http://dx.doi.org/10.1007/s00401-013-1092-y> (PMID: 23404369).
- Ng, M.F., 2010. The role of mast cells in wound healing. *Int. Wound J.* 7, 55–61. <http://dx.doi.org/10.1111/j.1742-481X.2009.00651.x> (PMID: 20409251).
- Okuse, K., 2007. Pain signalling pathways: from cytokines to ion channels. *Int. J. Biochem. Cell Biol.* 39, 490–496. <http://dx.doi.org/10.1016/j.biocel.2006.11.016> (PMID: 17194618).
- Pang, X., Letourneau, R., Rozniecki, J.J., Wang, L., Theoharides, T.C., 1996. Definitive characterization of rat hypothalamic mast cells. *Neuroscience* 73, 889–902. [http://dx.doi.org/10.1016/0306-4522\(95\)00606-0](http://dx.doi.org/10.1016/0306-4522(95)00606-0) (PMID: 8809807).
- Peng, W.M., Maintz, L., Allam, J.P., Raap, U., Güttgemann, I., Kirfel, J., Wardelmann, E., Perner, S., Zhao, W., Fimmers, R., Walgenbach, K., Oldenburg, J., Schwartz, L.B., Novak, N., 2013. Increased circulating levels of neurotrophins and elevated expression of their high-affinity receptors on skin and gut mast cells in mastocytosis. *Blood* 122, 1779–1788. <http://dx.doi.org/10.1182/blood-2012-12-469882> (PMID: 23869086).
- Poglio, S., De Toni-Costes, F., Arnaud, E., Laharrague, P., Espinosa, E., Casteilla, L., Cousin, B., 2010. Adipose tissue as a dedicated reservoir of functional mast cell progenitors. *Stem Cells* 28, 2065–2072. <http://dx.doi.org/10.1002/stem.523> (PMID: 20845475).
- Porzionato, A., Macchi, V., Parenti, A., De Caro, R., 2004. The distribution of mast cells in the human area postrema. *J. Anat.* 204, 141–147. <http://dx.doi.org/10.1111/j.1469-7580.2004.00256.x> (PMID: 15032921).
- Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmächer, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. *Arch. Gen. Psychiatry* 58, 445–452. <http://dx.doi.org/10.1001/archpsyc.58.5.445> (PMID: 11343523).
- Shanas, U., Bhasin, R., Sutherland, A.K., Silverman, A.J., Silver, R., 1998. Brain mast cells lack the c-kit receptor: immunocytochemical evidence. *J. Neuroimmunol.* 90, 207–211. [http://dx.doi.org/10.1016/S0165-5728\(98\)00137-4](http://dx.doi.org/10.1016/S0165-5728(98)00137-4) (PMID: 9817449).
- Silver, R., Curley, J.P., 2013. Mast cells on the mind: new insights and opportunities. *Trends Neurosci.* 36, 513–521. <http://dx.doi.org/10.1016/j.tins.2013.06.001> (PMID: 23845731).
- Smith, J.H., Butterfield, J.H., Pardanani, A., Deluca, G.C., Cutrer, F.M., 2011. Neurologic symptoms and diagnosis in adults with mast cell disease. *Clin. Neurol. Neurosurg.* 113, 570–574. <http://dx.doi.org/10.1016/j.clineuro.2011.05.002> (PMID: 21664760).
- Theoharides, T.C., Kempuraj, D., Tegen, M., Conti, P., Kalogeromitros, D., 2007. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol. Rev.* 217, 65–78. <http://dx.doi.org/10.1111/j.1600-065X.2007.00519.x> (PMID: 17498052).
- Turygin, V.V., Babik, T.M., Boyakov, A.A., 2005. Characteristics of mast cells in the choroid plexus of the ventricles of the human brain in aging. *Neurosci. Behav. Physiol.* 35, 909–911. <http://dx.doi.org/10.1007/s11055-005-0144-8> (PMID: 16270171).
- Valent, P., Horny, H.-P., Li, C.Y., Longley, J.B., Metcalfe, D.D., Parwaresch, R.M., Bennett, J.M., 2001. Mastocytosis. In: Jaffe, E.S., Harris, N.L., Stein, H., Vardiman, J.W. (Eds.), *World Health Organization (WHO) Classification of Tumours. Pathology and Genetics. Tumours of Haematopoietic and Lymphoid Tissues*. IARC Press, Lyon, pp. 291–302.
- Valent, P., Akin, C., Escribano, L., Födinger, M., Hartmann, K., Brockow, K., Castells, M., Sperr, W.R., Klün-Nelemans, H.C., Hamdy, N.A., Lortholary, O., Robyn, J., van Doormaal, J., Sotlar, K., Hauswirth, A.W., Arock, M., Hermine, O., Hellmann, A., Triggiani, M., Niedoszytko, M., Schwartz, L.B., Orfao, A., Horny, H.P., Metcalfe, D.D., 2007. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur. J. Clin. Invest.* 37, 435–453. <http://dx.doi.org/10.1111/j.1365-2362.2007.01807.x> (PMID: 17537151).
- Valent, P., Akin, C., Arock, M., Brockow, K., Butterfield, J.H., Carter, M.C., Castells, M., Escribano, L., Hartmann, K., Lieberman, P., Niedoszytko, B., Orfao, A., Schwartz, L.B., Sotlar, K., Sperr, W.R., Triggiani, M., Valenta, R., Horny, H.-P., Metcalfe, D.D., 2012. Definitions, criteria, and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int. Arch. Allergy Immunol.* 157, 215–225. <http://dx.doi.org/10.1159/000328760> (PMID: 22041891).
- Zarrindast, M.R., Valizadegan, F., Rostami, P., Rezayof, A., 2008. Histaminergic system of the lateral septum in the modulation of anxiety-like behaviour in rats. *Eur. J. Pharmacol.* 583, 108–114. <http://dx.doi.org/10.1016/j.ejphar.2008.01.003> (PMID: 18275952).