Mastocytosis: Determinants of Cognitive Complaints

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Abstract

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Cognitive complaints are reported to co-occur with Mastocytosis, a disease characterized by clonal proliferation of abnormal mast cells. Whether these cognitive complaints can be linked to the disease directly or may rather be attributed to psychological factors (emotional distress, fatigue and coping) is currently unknown. This study investigated neuropsychological symptoms in mastocytosis, using self-report data and physiological markers, to gain more insight in possible associations with, and predictors of, cognitive complaints, mental and physical fatigue in Mastocytosis. The sample consisted of 234 subjects with Mastocytosis, consulted via the University Medical Centre Groningen. Significant predictors of cognitive complaints were depression, fatigue and passive coping. Symptoms and sBT could not predict cognitive complaints in mastocytosis. Variation in mental and physical fatigue was accounted for by mastocytosis symptoms, depression and avoidant coping. Findings indicate that depression, mental fatigue and passive coping may play a particularly crucial role in subjective cognitive functioning. Fatigue in mastocytosis may be a symptom of depression as well as a consequence of mast cell burden directly.

Introduction

Mastocytosis is a multifaceted disease characterized by clonal proliferation of abnormal mast cells. It is a rare disorder and estimated to affect at least 13 per 100.000 people (van Doormaal et al.,2013). Symptoms are not only due to accumulation of mast cells in organs, but also due to the (chronic) release of all kinds of mediators (Di Mauro et al., 2021). For a diagnosis of mastocytosis, at least one major and one minor or three minor criteria must be met. The major criterion includes the presence of at least 2 dense infiltrates of mast cells (15 or more in aggregates) in bone marrow and/or other organs. Minor criteria entail, firstly, that more than 25% of mast cells are atypical cells, secondly, that a KIT-point mutation at codon 816 is present, thirdly, that immunohistochemical markers CD2 and/or CD25 and/or CD30 are present, and lastly, that serum baseline tryptase level (sBT) exceeds 20ng/mL (Valent et al., 2021). Mastocytosis symptoms can have a large impact on daily life, moreover, a substantial group also reports cognitive complaints.

The pathogenic mechanism of mastocytosis is likely a point mutation of the receptor tyrosine kinease KIT; in most cases a D816V-KIT mutation. Typically, the stem cell factor binds to KIT to stimulate normal growth, proliferation and differentiation. In mastocytosis, the KIT mutation results in constant overactivation of the receptor, signaling mast cells to proliferate excessively (Carter et al., 2014; Reiter et al., 2020). Mast cells store and release mediators, typically needed for an immune response e.g. in case of acute infections or allergy. Abnormal amounts act inflammatory, encourage development of hypersensitivities and can induce acute as well as chronic symptoms (Castells, 2006).

The site of mast cell accumulation and resulting symptoms vary highly, creating the heterogenous phenotype of the disease. The most common feature is cutaneous mastocytosis, often developed during childhood, causing skin lesions and symptoms like itching and flushing. The more severe form, Indolent Systemic Mastocytosis (ISM), entails, in addition to

skin lesion, dense infiltrates of mast cells in other organs, such as the liver, intestines, lymph nodes and almost always in the bone marrow (Pardanani et al 2019). Bone marrow mastocytosis (BMM) is defined as a subtype of systemic mastocytosis, characterized by isolated bone marrow involvement without skin lesions; most patients have a low burden of neoplastic mast cells and often normal or near normal sBT. Symptoms are the results of either chronic infiltration and/or the excessive releasability of the mast cells, as well as the chronic release of mediators. Symptoms include gastro-intestinal manifestations, such as, nausea, diarrhea, abdominal pain, cardiovascular instability and musculoskeletal pain, as well as a broad range of neurocoginitve symptoms like chronic fatigue, brain fog and headaches. Additionally, mastocytosis is associated with osteoporosis, especially fragility fractures and episodes of anaphylaxis (Pardanani et al., 2021).

Even though symptoms are mainly induced by chronic mediator release of, among others, tryptase and histamine, the extent to which mediators play a role in the different symptoms of mastocytosis is not yet fully understood. sBT is frequently elevated in mastocytosis patients. sBT has previously been reported as the most sensitive marker of mastocytosis because its levels are associated with the total mast cell burden as well as bone marrow involvement, possibly even indicate progression of the disease. However, there is no clear correlation between sBT and symptoms of mastocytosis. Moreover, only 85% of mastocytosis patients show elevated sBT in the first place. Thus, even though prognostic value for symptoms based of mediator levels is limited to date, it is hypothesized that elevated plasma histamine and/or tryptase levels could be considered as a potential cause, not only for physical symptoms, but also for cognitive complaints. (Matit et al., 2013; Pardanani et al., 2018; Quintas-Cardama et al., 2013).

It has become increasingly evident that mastocytosis symptoms can also entail cognitive complaints. Also often labeled as brain fog, they are common among mastocytosis

patients (74%, N=57) (Moura et al., 2012). Complaints are mostly reported in the domains of memory and attention and tend to fluctuate in accordance with other symptoms of the disease. Brain imaging has indeed shown punctuated white matter brain abnormalities in just above 40% of both cutaneous and indolent systemic mastocytosis patients (Boddaert et al., 2017). Clear differentiations between cognitive complaints and cognitive impairments should be considered. While complaints are subjectively reported by the patient, impairments are objectively diagnosed in neuropsychological assessment. In a cohort of 139 subjects, 52% expressed subjective complaints about episodes of memory loss and 40% experienced difficulty concentrating (Jendoubi et al., 2021). Yet, among 42 patients who reported subjective cognitive complaints, 22 were indeed objectively diagnosed with cognitive impairment (Moura et al., 2012). More specifically, working memory was found to be impaired in 73% (n=16) and immediate auditory memory in 41% (n=9) out of the 22 subjects (Moura et al., 2012). It remains unclear to what extent actual cognitive impairments may underly cognitive complaints in Mastocytosis. Multiple potential causes for cognitive complaints in mastocytosis have been suggested. Jendoubi et al (2021) proposed that the release of mediators may act neurotoxic, possibly causing direct neuronal death and neurodegeneration. Mast cells in the brain are located in, among others, the area postrema, the thalamus and hypothalamus. Mast cells are involved in neuroimmunoendocrine responses, linking the brain with the immune system. In response to physical or psychological stress via the hypothalamic pituitary adrenal (HPA) axis, mast cells degranulate, thereby releasing histamine and corticotropin-releasing hormone (CRH) (Traina, 2019, Dong et al., 2021). This is in line with the observation that sometimes, cognitive complaints in mastocytosis could be alleviated by anti-histamines (Jendoubi et al., 2021). The degranulation of mast cells may increase the permeability of the blood brain barrier, and has been linked to perioperative cognitive dysfunction as well as, cognitive processes in multiple

sclerosis, Alzheimer's and Parkinson's disease (Dong et al., 2021, Kempuraj et al., 2019). Cognitive complaints were not found to be associated with the type of Mastocytosis, present skin lesions, nor with gender (Jendoubi et al. 2021), although it has previously been suggested, that females may be more prone to suffer cognitive complaints in mastocytosis than males, due to the involvement of mast cells in the neuroendocrine regulation (Moura et al., 2012). Thus, neurotoxicity could be a potential cause for possible brain injury, accounting for cognitive complaints in mastocytosis. However, also other psychosocial factors such as emotional distress or fatigue may account for cognitive complaints (Vermeiren et al., 2020). Alltogether, the relationship between cognitive complaints and cognitive impariments is complex and not yet understood in mastocytosis.

Cognitive complaints in Mastocytosis may partly be accounted for by emotional symptoms of depression and anxiety. Mastocytosis is associated with emotional distress, more specifically, low mood, irritability, dissatisfaction, guilt, self-doubt, frustration, somatic and psychic anxiety, lack of initiative and lack of motivation. In total, prevalence of depression and anxiety symptoms in mastocytosis is 30% to 64%, some findings even suggest a prevalence of up to 70% (Vermeiren et al.,2020). Prevalence of moderate depression symptoms is high (56%, N=288), severe symptoms of depression have been reported 8% (N=288) and 30% (N=39). From this the question derives, if physical symptoms are the main cause for emotional distress. Alternatively, skin lesions (physical appearance) may act as an additional burden, thereby increasing distress and ultimately influence cognitive complaints. It has yet to be determined if cognitive complaints and emotional distress differ among ISM and BMM diagnoses. While gender differences regarding emotional distress in mastocytosis are relatively unexplored, it is known that females tend to have elevated rates of depression compared to males in chronic pain conditions such as fybromyalgia (Munce et al., 2007). In general, scores of Mastocytosis patients on the SCL-90, assessing symptoms of emotional

distress, were found to be lower than scores of chronic pain patients (Vermeiren et al., 2020). However, depressive symptoms in mastocytosis seem to occur more frequently compared to other chronic diseases such as advanced diabetes, with a depression prevalence of 14%-25%. Moreover, depression in Mastocytosis appeared to be independent of objective physical impact of the disease (Moura et al., 2011,). Therefore, it is possible that depression in mastocytosis may be directly associated to mast cell activation rather than to the burden of having a chronic debilitating disease. In support of this claim, brain imaging showed punctuated white matter abnormalities in 49% (N=39). Furthermore, depressed mastocytosis patients showed elevated putamen perfusion as well as diminished subgenual cingulate cortex perfusion, an area known to play a key role in emotion regulation (Boddaert et al., 2017, Georgin-Lavialle et al., 2016, Hermine et al., 2008, Moura et al., 2011, Jendoubi et al., 2021).

Another frequent symptom of Mastocytosis is fatigue. While fatigue is known to be a symptom of depression, it can also be linked to mastocytosis directly. Fatigue has been observed to fluctuate with disease level indicating that released mediators may account for feeling fatigued (Vikse et al., 2019). Generally speaking, literature documents an association of depression with objective cognitive impairments in attention, short-term memory and executive functioning (Murrough et., 2011). However, in mastocytosis depressive symptoms and cognitive impairments were previously found to be independent of each other (Moura et al., 2012). Thus, the nature of emotional distress and fatigue in mastocytosis, as well as the association of these symptoms with cognitive complaints remains uncertain. In order to determine if cognitive symptoms may indeed be associated with fatigue or emotional distress, it is also of interest to control for coping style. Among others, three coping styles are frequently considered to differentiate the ability of dealing with a stressful situation, namely, passive reactive, active tackling and avoidant coping style. Active coping entails to intentionally reduce physical, psychological or social stress by making goal-directed efforts

(Folkman & Lazarus, 1991). A Passive coping style describes behavior in which one withdraws from the responsibility to pro-actively reduce stressors and instead views them as external uncontrollable factors. Avoidant coping holds in to deny the cause of distress and keep efforts of dealing with the stressor at its minimum (Holahan et al., 2005). One's approach and ability to deal with stress can account for cognitive complaints. Coping styles have previously been reported to be associated with cognitive complaints in chronic pain patients (Roth et al., 2005). Moreover, proactive coping is reported to be associated with fewer cognitive complaints (Nijsse et al., 2015.) All of the above, namely feeling depressed, anxious, fatigued and dysfunctional coping may account for (part of the) cognitive complaints in Mastocytosis.

Overall, mastocytosis is classified as an immune disorder with moderate to high prevalence of neuropsychological symptoms (Moura et al., 2012; Georgin-Lavialle et al., 2016; Jendoubi et al., 2021). Common are cognitive complaints regarding memory and attention. Furthermore, high prevalence of emotional distress and fatigue can be observed among mastocytosis patients. To date, little research has been done to explore cognitive complaints in mastocytosis and associations of cognitive complaints with emotional distress and fatigue in Mastocytosis remain uncertain. Research in this field is of particular relevance, as many many ckit inhibitors of high cost are currently being developed, the most recent being avapritinib specifically targeting the D816V mutation, costing 350.000 euros per year. From this, the question arises, to what extent cognitive symptoms could be alleviated by therapy targeting psychosocial factors like emotional distress, fatigue and coping style, or if cognitive complaints are related to the disease directly, requiring appropriate medication.

The objectives of this study were to first investigate group differences, thereby raising the following two questions: Are there significant gender differences in mastocytosis symptoms, cognitive complaints, emotional distress, fatigue and coping style? Are there

significant differences in type of diagnosis (ISM or BMM) in cognitive complaints, emotional distress, fatigue and coping style? Secondly, the aim was to test for associations which brings into question: To what extent are cognitive complaints associated with mastocytosis symptoms, emotional distress, fatigue, coping style and sBT levels? Finally, the objective is to test for predictors of cognitive complaints, mental and physical fatigue, more specifically the following three questions were being raised: To what extent can symptoms, emotional distress, fatigue and coping style account for variation in cognitive complaints? To what extent can symptoms, emotional distress and coping style account for variation in mental fatigue? And lastly, to what extent can symptoms, emotional distress and coping style account for variation in physical fatigue?

Methods

Participants

This study acquired data from patients with mastocytosis living in the Netherlands, that are being or have been treated by the expertise centrum of the University Medical Centre Groningen (UMCG). Subjects were recruited in collaboration with Dr. H.N.G. Oude Elberink, allergist with expertise in mastocytosis, director of the Dutch Mastocytosis Expert Centre Groningen (NMCG). Patients of age 18 or above were included in the study if the have been diagnosed with mastocytosis by bone marrow biopsy. They must fulfill the criteria of having at least one major and one minor or three minor criteria of SM. Patients were diagnosed having ISM or BMM. Moreover, patients with the diagnosis Mastocytosis in the skin (MIS) were included, referring to a condition with skin lesions, when the patient has not yet been evaluated for a diagnosis of ISM. A diagnosis of cutaneous mastocytosis (MPCM) entails skin lesions only.

Design

The study was conducted from April 2022 to June 2023. The research consisted of self-report questionnaires, namely: The Mastocytosis Quality of Life questionnaire, the Mastocytosis Klachten lijst, the Cognitive Failure questionnaire, the Groninger Cognitie lijst, the Dutch Multifactor Fatigue scale and the Utrecht's Coping lijst . Items of the questionnaires were transcribed into an online database system (redcap) to send out as a survey via email. A total of three reminders were sent if they had not or had only partially responded. Data were collected in compliance with the ethical regulations of the UMCG.

Measures

Mastocytosis Symptoms

The Mastocytosis Symptom Assessment Form also called Mastocytosis Klachten lijst (MKL) is a 24-item questionnaire of which 10 items were used in this study to asses physical symptoms of mastocytosis. The items measuring fatigue were excluded because the Dutch Multifactorial fatigue assessment form addresses fatigue sufficiently. Symptom severity is scored on a scale from 1-10, total scores range from 0 to 100.

The questionnaire Mastocytose Kwaliteit van Leven vragenlijst (MQLQ) (van Anrooij et al., 2016) consists of 50 items measuring symptoms of Mastocytosis and to what extent they have an impact on the quality of life. It is scored on a seven-point scale from “does not apply” to “very much”. Total scores range from 0 to 600.

Cognitive Complaints

The Groninger Cognitielijst (GroCo) consists of 11 items measuring cognitive complaints on a 4-point scale from “not at all” to “very much” with total scores from 0 to 33.

The Cognitive Failure Questionnaire (CFQ) assess cognitive functioning in daily life. It consists of 25 items with a 5-point scale from “very often” to “never”. It is scored on 4 subscales that are absent-mindedness”, “absent-mindedness in social situations”, “names and words” and “orientation”. Total scores range from 0 to 100.

Emotional distress

The Hospital Anxiety and Depression scale (HADS) (Zigmond & Snaith et al., 1983) is a 14-item questionnaire that measures anxiety and depression on a likert scale from 0 to 3. It is scored on the two subscales Anxiety and Depression with 7 items each. Total scores ranging from 0 to 21. Scores from 0 to 7 are considered normal, from 8 to 10 mild to moderate depression and above 11 scores indicate considerable depression and/or anxiety.

Fatigue

The Dutch Multifactor Fatigue Scale (DMFS) (Visser-Keizer et al., 2015) measures symptoms of fatigue during the past month. It consists of 38 claims and is measured on a 5-point scale from “totally disagree” to “fully agree”. Two out of the five subscales are being used in the current study which are mental fatigue with possible scores ranging from 7 to 35 and physical fatigue with scores ranging from 6 to 30.

Coping style

The Utrechtse coping lijst (UCL) (Schreurs et al., 1993) measures coping style with 47 items scored on a scale from 1 to 4. From the seven subscales, three were included in the present study, which are active coping (7 items, range 7-28), avoiding (8 items, range 8-32) and passive coping (7 items, range 7-28).

Data analysis

SPSS was used to analyze data. Subjects who did not fill in the questionnaires after three reminders have been excluded from the analysis. Outliers were included as they are a natural part of the population being studied. Descriptive statistics are performed to describe the sample in gender, age, educational level and type of mastocytosis. Assumptions were checked. Independent sample t-tests to test for gender differences are performed on the MKL, MQLQ, CFQ, GroCo, HADS, DMFS and UCL passive reactive, active tackling and avoidant coping style. Independent t-tests are also conducted to examine differences in ISM and BMM diagnosis on the above-described measures. A correlational analysis is conducted to investigate associations of mastocytosis symptoms (MKL), cognitive complaints (GroCo) and sBT with emotional distress, fatigue and coping style. Pearson correlations were conducted for all variables except for the variable sBT levels, which were being analyzed non-parametrically with Spearman’s correlation. Finally three multiple regression analysis are

performed to first predict cognitive complaints, secondly to predict mental fatigue and third, to predict physical fatigue

Results

Participants

Table 1 presents the descriptive statistics. In total, 234 responded to the survey from which 20 patients did not finish the first questionnaire about Mastocytosis symptoms and were excluded. Thus, the sample consists of 214 subjects (M age = 58.2 years, SD = 13.5).

Table 1

Demographic Characteristics, n=214

Variable	
Gender, female, n (%)	130 (61)
Age, M(SD)	58.2 (13.5)
Education, M(SD)	5.4 (1.1)
Mastocytosis, n (%)	
ISM	126 (59)
BMM	51 (24)
MIS	12 (6)
MPCM	10 (5)
Other	11 (5)
Unknown	4 (2)

Note. Education = 7-point scale ranging from 1 (*primary school education*) to 7 (*university education*) ISM = Indolent systemic Mastocytosis, BMM = Bone Marrow Mastocytosis, MIS = (Skin lesions, unknown ISM, MPCM = Cutaneous Mastocytosis (Skin lesions only)

Gender differences

Table 2 presents the results from the independent samples t-tests that were performed to test for gender differences in Mastocytosis symptoms, cognitive complaints, anxiety, depression,

fatigue and coping styles. Females suffered from significantly more symptoms of Mastocytosis than males according to both the MKL and the MQLQ general symptoms subscale. Females reported significantly more cognitive complaints according to the CFQ, however no significant gender differences were detected by the GroCo. Females reported significantly higher levels of avoidant coping than males. No significant gender differences were found for passive coping or active coping. Females experienced significantly higher levels of fatigue, both physically and mentally, than males according to the DMFS. No gender differences were present for emotional distress.

Table 2

Gender differences in mastocytosis symptoms, cognitive complaints, emotional distress, fatigue and coping style.

Variable	Male	*Female*	*t(212)*	*p*	Cohen's
	M (SD)	*M (SD)*			*d*
Mastocytosis symptoms					
MKL	18.67 (14.3)	27.6 (17)	-3.98	**<.001**	-.56
MQLQ (general)	13.07 (8)	16.9 (8.7)	-3.27	**<.001**	-.46
Cognitive complaints					
CFQ	38.9 (12.7)	43.6 (13.1)	-2.59	**<.05**	-.36
GroCo	10.3 (7.2)	11.2 (7.3)	-.9	0.372	-.13
Emotional distress (HADS)					
Anxiety	5.3 (3.8)	6.3 (4.4)	-1.67	.096	-.24
Depression	4.5 (3.9)	4.8 (4)	-.37	.71	-.05
Fatigue (DMFS)					
Mental fatigue	20.6 (6.9)	24.5 (6.5)	-4.2	**<.001**	-.59

Physical fatigue	17.7 (6.2)	20.4 (6)	-3.09	**<.01**	-.44
Coping (UCL)					
Active tackling	17.9 (3.9)	18.2 (3.5)	-.71	.482	-.1
Avoiding	15.3 (3.5)	16.8 (3.4)	-3.02	**<.01**	-.43
Passive reacting	11.5 (3.4)	12 (3.7)	-.89	.376	-.13

Note. MKL = Mastocytosis symptom list, MQLQ = Mastocytosis quality of life questionnaire, CFQ = Cognitive failure questionnaire, GroCo = Groninger Cognition list, HADS = The Hospital Anxiety and Depression scale, DMFS = Dutch Multifactor Fatigue Scale, UCL = Utrechtse coping list.

Group differences in ISM and BMM

Table 3 presents differences in Indolent Systemic Mastocytosis (ISM) and Bone Marrow Mastocytosis (BMM). No significant differences among those two mastocytosis diagnoses were found in cognitive complaints, emotional distress, fatigue or coping styles. Findings are displayed below in table 3.

Table 3

Group differences of Indolent Systemic Mastocytosis and Bone marrow mastocytosis in cognitive complaints, emotional distress, fatigue and coping style

Variable	*ISM*	*BMM*	*t(212)*	*p*	Cohen's
	M (SD)	*M (SD)*			*d*
	N=212	*N=212*			
Cognitive Complaints					
CFQ	42.1 (12.7)	38.6 (12.2)	1.763	.096	.278
GroCo	11 (7.2)	9.8 (7.3)	.948	.348	.158

Emotional distress					
Depression	4.5 (4.1)	4.5 (4.1)	.03	.976	.005
Anxiety	5.8 (4.3)	5.4 (3.7)	.587	.558	.098
Fatigue DMFS					
Mental fatigue	23.2 (6.4)	21.3 (7.4)	1.762	.08	.293
Physical fatigue	19.7 (5.6)	17.9 (7.)	1.744	.083	.290
Coping					
UCL Active tackling	18.2 (3.5)	17.7 (4.2)	.79	.43	.133
UCL Avoiding	16.4 (3.3)	15.5 (3.8)	1.369	.175	.245
UCL passive reacting	11.8 (3.7)	11.4 (3)	.715	.475	.12

Note. MKL = Mastocytosis symptom list, MQLQ = Mastocytosis quality of life questionnaire, CFQ = Cognitive failure questionnaire, GroCo = Groninger Cognition list, HADS = The Hospital Anxiety and Depression scale, DMFS = Dutch Multifactor Fatigue Scale, UCL = Utrechtse coping list.

Correlations of Mastocytosis symptoms, Cognitive complaints and Tryptase with emotional distress, fatigue and coping styles.

Table 4 presents the correlation coefficients between mastocytosis symptoms, cognitive complaints and tryptase levels with emotional distress, fatigue and coping styles. Symptoms of mastocytosis are highly significantly positively correlated with anxiety, mental fatigue, physical fatigue and a passive reactive coping style. Symptoms of Mastocytosis have a significantly positive correlation of moderate size with cognitive complaints depression, and an avoidant coping style. Cognitive complaints are highly significantly positively associated with mental fatigue and a passive reacting coping style. Moderate to high correlations of cognitive complaints with emotional distress are found to be significantly positively with anxiety and depression. No significant correlations were found between tryptase and these measures of symptoms, cognitive complaints, emotional distress nor coping styles.

Table 4

Correlations of symptoms, cognitive complaints and tryptase levels with anxiety, depression, physical and mental fatigue and coping style.

Variable	MKL N=214	CFQ N=214	GroCo N=214	Tryptase N=202
1. Symptoms (MKL)	—	.46**	.48**	ρ = -.01
2. Cognitive complaints (CFQ)	.46**	—	.71**	ρ = .09
3. Cognitive complaints (GroCo)	.48**	.71**	—	ρ = .08
4.Tryptase	-.01	.08	.10	—
5. Anxiety (HADS)	.52**	.49**	.55**	ρ = -.03
6. Depression (HADS)	.42**	.51**	.61**	ρ = -.00
7. Mental fatigue (DMFS)	.61**	.61**	.68**	ρ = -.02
8. Physical fatigue (DMFS)	.65**	.49**	.53**	ρ = -.02

9. Passive reacting (UCL)	.51**	.56**	.64**	ρ = -.03
10. Avoiding (UCL)	.37**	.39**	.47**	ρ = -.05
11. Active tackling (UCL)	.03	.05	-.10	ρ = -.08

Note: **Correlation is significant at 0.01 level (2-tailed), N=214, tryptase N=194 after excluding outliers. MKL = Mastocytosis symptom list, MQLQ = Mastocytosis quality of life questionnaire, CFQ = Cognitive failure questionnaire, GroCo = Groninger Cognition list, HADS = The Hospital Anxiety and Depression scale, DMFS = Dutch Multifactor Fatigue Scale, UCL = Utrechtse coping list.

Predictors of cognitive complaints

A multiple linear regression to predict cognitive complaints measured by the GroCo, yields a non-significant model (R = .14, p = .30) of the first block explaining. The predictors gender, education and age account for 2% of the variation in cognitive complaints.

The second block model, with Mastocytosis symptoms as a predictor, is statistically significant (R = .49, p<.001) and accounts for 24% of the variation in cognitive complaints. There is a significant increase in explained variance from model 1 to model 2 (F change = 54.28, p<.001). The third block model in which the predictors anxiety, depression, physical fatigue, mental fatigue, avoidant coping style and passive reactive coping style were added, is statistically significant (R=.77, p<.001) and accounts for 60% of the variation in cognitive complaints. There is a significant increase in explained variance from model 2 to model 3 (F Change = 27.64, p<.001).

Table 5

Multiple regression predicting cognitive complaints (GroCo)

	95% CI

Variable	Beta	SE	LL	UL	ß	*p*
Step 1						
Constant	15.85	2.92	10.10	21.61	-	<.001
Education	-1.18	1.75	-4.64	2.27	-.05	.501
Gender	-.57	1.09	-2.73	1.59	-.04	.603
Age	-.06	.04	-.14	.01	-.12	.108
Step 2						
Constant	6.69	2.87	1.04	12.35	-	<.05
Education	-.23	1.56	-3.29	2.84	-.01	.885
Gender	1.01	.99	-.95	2.96	.07	.310
Age	-.02	.04	-.09	.05	-.04	.532
Symptoms	.22	.03	.16	.28	.49	<.001
Step 3						
Constant	-10.98	3.06	-17.01	-4.95	-	**<.001**
Education	-.02	1.17	-2.33	2.28	-.00	.984
Gender	1.24	.76	-.26	2.74	.08	.104
Age	.02	.03	-.04	.07	.03	.518
Symptoms	.02	.03	-.04	.08	.04	.549
Emotional distress						
Depression	.42	.13	.16	.68	.23	**<.01**
Anxiety	-.06	.14	-.33	.22	-.03	.687
Fatigue						
Mental	.47	.08	.31	.63	.45	**<.001**
Physical	-.11	.09	-.29	.07	-.09	.239
Coping style						
Avoiding	.24	.12	-.01	.47	.12	.042
Passive	.49	.16	.18	.81	.24	**<.01**

Note. Cognitive complaints = GroCo, emotional distress = HADS, fatigue = DMFS, coping = UCL

Predictors of mental fatigue

A multiple linear regression to predict mental fatigue, yields a significant model (R=.32, p<.001) of the first block explaining 10% of the variance in mental fatigue. The predictors gender, education and age account for 10% of the variation in mental fatigue. The second block model, including MKL symptoms as a predictor, is statistically significant (R=.65, p<.001) and accounts for 42% of the variance in cognitive complaints. There is a significant increase in explained variance from model 1 to model 2 (F Change = 102.44, p<.001). The third model, with addition of the predictors anxiety, depression, avoidant coping style and passive reactive coping style, is statistically significant (R=.75, p<.001) and accounts for 56% of the variation in cognitive complaints. There is a significant increase in explained variance from model 1 to model 2 (F Change = 15.83, p<.001).

Table 6

Multiple regression predicting mental fatigue

Variable	Beta	SE	95% CI		ß	*p*
			LL	UL		
Step 1						
Constant	30.38	2.70	25.06	35.70	-	<.001
Education	-1.36	1.62	-4.55	1.83	-.06	.401
Gender	-3.43	1.01	-5.42	-1.44	-.24	<.001
Age	-.08	.04	-.16	-.01	-.16	<.05
Step 2						
Constant	19.76	2.42	14.98	24.53	-	<.001
Education	-.25	1.31	-2.84	2.34	-.01	.848
Gender	-1.60	.84	-3.25	.05	-.11	.057
Age	-.035	.03	-.09	.02	-.07	.235
Symptoms	.25	.03	.20	.30	.59	<.001
Step 3						
Constant	10.09	2.89	4.39	15.80	-	<.001
Education	.01	1.16	-2.29	2.31	.00	.993
Gender	-1.90	.75	-3.37	-.43	-.13	**<.05**
Age	-.01	.03	-.07	.04	-.02	.666
Symptoms	.15	.03	-.10	.20	.34	**<.001**
Emotional distress						
Depression	.40	.12	.16	.64	.23	**<.01**
Anxiety	.07	.14	-.20	.34	.04	.616
Coping style						
Avoiding	.33	.11	.103	.55	.17	**<.01**
Passive	.27	.16	-.04	.58	.14	.088

Note. Cognitive complaints = GroCo, emotional distress = HADS, fatigue = DMFS, coping = UCL

Predictors of physical fatigue

A multiple linear regression to predict physical fatigue, yields a significant model (R=.25, p<.05) of the first block explaining 6% of the variation in physical fatigue.

The second block model, including the predictor MKL symptoms, is statistically significant (R=.66, p=<.001) and explains 44% of the variance in physical fatigue. There is a significant increase in explained variance from model 1 to model 2 (F change = 127.54). The third model, which includes anxiety, depression, avoidant coping style and passive reactive coping style, is statistically significant (R=.75, p<.001) and accounts for 56% of the variation in physical fatigue. There is a significant increase in explained variance from model 2 to model 3 (F Change = 13.56, p<.001).

Table 7

Multiple regression predicting physical fatigue.

			95% CI			
Variable	Beta	SE	LL	UL	ß	*p*
Step 1						
Constant	25.40	2.47	20.54	30.27	-	<.001
Education	-2.46	1.48	-5.38	.46	-.12	.098
Gender	-2.08	.92	-3.90	-.25	-.16	<.05
Age	-.053	.03	-.12	.013	-.11	.114
Step 2						

Constant	14.99	2.13	10.79	19.18	-	<.001
Education	-1.38	1.15	-3.65	.90	-.07	.234
Gender	-.28	.74	-1.73	1.17	-.02	.700
Age	-.01	.03	-.06	.05	-.01	.832
Symptoms	.25	.02	.20	.29	.64	<.001
Step 3						
Constant	11.12	2.59	6.01	16.23	-	<.001
Education	-.73	1.04	-2.79	1.33	-.04	.485
Gender	-.62	.67	-1.93	.70	-.05	.358
Age	-.01	.02	-.06	.04	-.02	.779
Symptoms	.18	.02	.13	.22	.46	**<.001**
Emotional distress						
Depression	.62	.11	.40	.83	.39	**<.001**
Anxiety	-.10	.12	-.34	.14	-.06	.431
Coping style						
Avoiding	.17	.10	-.03	.37	.09	.103
Passive	.02	.14	-.26	.30	.01	.896

Note. Cognitive complaints = GroCo, emotional distress = HADS, fatigue = DMFS, coping = UCL

Discussion

The purpose of this study was to gain better understanding of cognitive complaints as well as of emotional distress, fatigue and coping style among mastocytosis patients. Overall, among the entire group, it was found that psychological factors may account for cognitive complaints in mastocytosis, while cognitive complaints could not be linked to the disease directly. Significant predictors of cognitive complaints were depression, fatigue and passive coping. Symptoms and sBT could not to predict cognitive complaints in mastocytosis. Variation in mental and physical fatigue was accounted for by mastocytosis symptoms, depression and avoidant coping. Thus, total must cell burden may not be associated with cognitive complaints directly. There seems to be no indication of underlying objective cognitive impairment in mastocytosis. Rather, mastocytosis can cause stress and mental fatigue, which may ultimately lead to subjective cognitive complaints.

Findings of gender differences in cognitive complaints were found for one measure of cognitive functioning (CFQ). Furthermore, women suffer significantly more from somatic symptoms of the disease, but against expectations, not significantly more from anxiety, nor depression. Literature reports higher prevalence of depression in women across the general population, as well as in chronic pain conditions such as fibromyalgia, arthritis/rheumatism, back problems and migraines, whereas in cancer no significant gender differences were reported. This suggests that the prevalence of emotional distress may depend on the type of chronic disease and may be equal among men and women in mastocytosis. (Munce et al., 2007, Shanmugasegaram et al 2012).

No differences were observed between ISM and BMM, indicating that bone marrow mastocytosis without skin lesions, compared to bone marrow mastocytosis with present skin lesions, seems not to cause differences in cognitive complaints. Also, emotional distress does not differ between these two diagnoses, suggesting that skin lesions/physical appearance

seem not to majorly add to emotional distress. Since the sample size of MPCM, which entails skin lesions only, was too small, the present study was unable to explore differences between systemic mastocytosis and cutaneous mastocytosis; possibly interesting for future directions.

The present study partially supports the hypothesis that mental distress, i.e. feeling depressed, anxious and/or fatigued, may account for an important part of the cognitive complaints in Mastocytosis. All of these factors correlate moderately with cognitive complaints. Depression, mental fatigue and passive coping can account for (60%) variation in cognitive complaints. Thus, mastocytosis may cause distress and fatigue, which may lead to cognitive complaints. Present findings of depression being associated with and predicting cognitive complaints, seem to counter the previous claim by Moura et al., (2012), who found supporting evidence for depressive symptoms being independent of cognitive impairment. However, comparability of these findings is in doubt, as the present study investigated cognitive complaints and not objective cognitive impairment. Anyhow, Jendoubi et al., (2021) found depression to be indeed associated with cognitive complaints in mastocytosis. To conclude, it is likely that cognitive complaints may be (partly) accounted for by depression. Regarding mental fatigue, it is plausible that perceived stress and emotional exhaustion is associated to subjective cognitive complaints, moreover, possibly leading to subjective cognitive decline (Zhang et al., 2023). Especially concentration and memory have previously been reported to be associated with fatigue and perceived stress because of health problems (Podlesek et al., 2021). Suboptimal coping styles (passive and avoidant) were associated with higher levels of cognitive complaints in the present study. Moreover, passive coping accounted for variation in cognitive complaints, hence, excessive worrying, feeling sad or helpless can evoke or increase cognitive complaints. An active coping style is not found to be associated with cognitive complaints, indicating that acceptance of the disease

and taking initiative to better manage/overcome stress may not necessarily alleviate cognitive complaints, which is not in line with previous results by Nijsse et al., (2015).

To some extent results are in favor of the premise that cognitive complaints are accounted for by the level of the disease directly, hence, by somatic symptoms. Symptoms were found to moderately correlate with cognitive complaints and significantly predict cognitive complaints when being added to the model solely. However, symptoms can no longer significantly account for cognitive complaints when emotional distress, fatigue and coping style are included. This indicates that these factors have overlapping explained variance with symptoms and are stronger predictors of cognitive complaints. Also, Jendoubi et al., (2021) found cognitive complaints to be independent of mast cell mediator related symptoms. To conclude cognitive complaints may indeed be associated with symptoms to some extent, but appear more strongly accounted for by other factors than by symptoms directly, such as depression, mental fatigue and passive coping.

sBT is not associated with cognitive complaints, nor with any of the factors assessed by the present study. This is in line with findings by Jendoubi et al (2021) reporting no association of indicators of total mast cell burden, such as sBT, with symptoms. Whether this means that somatic symptoms, cognitive complaints, emotional distress and fatigue are not directly associated with the level of the disease but rather result from the burden of being ill, or if the factors may be directly linked to other biomarkers/mediators such as methyl histamine (MH) or methylimidazolazijnzuur (MIMA), has yet to be determined.

Looking more closely at depression, present findings suggest that symptoms may be associated with depression, thereby contradicting the claim that depression may be independent of objective physical impact of mastocytosis (Moura et al., 2011). Jendoubi et al., (2021) found depression to be indeed associated with urinary and gastro-intestinal symptoms of mastocytosis. Therefore, it is unclear if depression results from the burden of

suffering somatic symptoms or if it results from mast cell activation directly. Since depression accounts for variance in cognitive complaints, it could be of interest for future directions to explore the nature of depression in mastocytosis further.

Fatigue is often viewed as a symptom of depression; however, it has been hypothesized that fatigue may be directly linked to mast cell mediator release. Indeed, depression is moderately associated with fatigue and significantly predicts both, mental and physical fatigue in the present study. However, also symptoms can account for mental and physical fatigue. This indicates that mental and physical fatigue may indeed be linked to mast cell burden, thus, mastocytosis directly. This is in line with the previous observation that fatigue may fluctuate with disease level, indicating that released mediators may account for feeling physically and mentally fatigued (Vikse et al., 2019). Regarding the association of avoidant coping with mental fatigue, it is plausible that when suffering from mental fatigue, one tends to avoid situations with many stimuli. Potential intervention implications would entail to target certain coping styles in therapy if approaches such as changing passive coping styles are found to effectively reduce cognitive complaints.

Limitations of this study are that results are based solely on self-report data except sBT. Self-reported somatic symptoms are therefore used as an indicator for mast cell burden in the analysis of present results, however self-reported symptoms may not accurately reflect objective mast cell burden when measured by mediator levels or bone marrow infiltration. Moreover, although coping has been considered, it remains unclear what other factors could influence perception of symptoms and cognitive complaints. No control group was included in the study, thereby not allowing for comparison of the results with the healthy population. It has yet to be determined if participants with mastocytosis would score significantly higher on cognitive complaints, emotional distress and fatigue compared to healthy controls.

Furthermore, it has to be investigated if cognitive complaints would correspond to objective cognitive impairment.

To conclude, somatic symptoms may account for cognitive complaints to some extent, however depression, mental fatigue and passive coping seem to play a particularly crucial role in subjective cognitive functioning. Fatigue can be accounted for by both, depression as well as somatic symptoms. This indicates that fatigue in mastocytosis may be a symptom of depression as well as a consequence of mast cell burden directly. Implications of this study are to increase knowledge among practitioners about cognitive complaints in mastocytosis, to provide targeted support and interventions for neuropsychological complaints.

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