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Clinical Psychology and Clinical Immunology: is there a link between Alexithymia and severe Asthma?

Luisa Ricciardi [1], Giovanna Spatari [2], Carmelo Mario Vicario [3], Marta Liotta [4], Valentina Cazzato [5], Sebastiano Gangemi [1], Gabriella Martino [1]*

Abstract

Background: Severe asthma patients are those suffering from asthma exacerbations despite adherence to maximal optimized asthma treatment such as high dose inhalant corticosteroids and long-acting beta2 agonists (ICS-LABA). It is estimated that about 300 million people in the world are affected from asthma and among them a percentage between 3-10% suffer from severe asthma. The prevalence of Alexithymia in chronic illness is notably high and it is strictly related to clinical severity of chronic diseases.

Methods: Pub Med and Google Scholar databases were consulted using the terms "severe asthma" AND "alexithymia" to search English-language articles. According to inclusion criteria 37 articles were finally included and analyzed. Alexithymia may interfere with the perception of the disease and the patients' awareness of the need of a strict follow-up, to adhere to the physicians' treatment plans.

Results: Alexithymia and related psychological distress as anxiety and depression may compromise the patient's compliance and adherence, leading to a severe clinical presentation and pathologies' course. This review highlights a potential relationship between alexithymia and severe asthma as a chronic inflammatory disease and the ways this correlation can be assessed and managed in the Outpatient Asthma Clinic to ensure a global approach to SA patients. Findings reported in literature suggest that, among severe asthma patients, alexithymia is present even if the prevalence of this disorder has not yet been defined.

Conclusions: It is likely that the introduction of a gold standard clinical psychological evaluation in medical settings, such as clinical allergy and immunology, may allow to support suffering patients helping them to adequately elaborate their particular condition developing useful strategies to control and to manage with their severe asthma.

[1] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[2] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[3] Department of Cognitive Sciences, Psychology, Education and Cultural Studies, University of Messina, Messina, Italy
[4] U.O. Allergology and Clinical Immunology, University Hospital of Messina, Messina, Italy
[5] School of Natural Sciences and Psychology, John Moores University, Liverpool, United Kingdom
E-mail corresponding author: luisa.ricciardi@unime.it

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1. Introduction

Asthma is a heterogeneous disease with an underlying chronic inflammation (GINA, 2021); as it is a chronic disease it is characterized by relapse and remission phases with symptoms such as shortness of breath and cough that sometimes are underestimated by patients and misinterpreted as lack of exercise, fatigue, or acute airway infection (Larsson, 2020). To further complicate the recognition of asthma affected patients, results from clinical examination, including chest auscultation, may be completely normal in remission phases still characterized by small airway inflammation (Li et al., 1996). Among patients affected by asthma, severe asthma (SA) is present in about 5-10% of patients; these patients experience poor symptom control despite adherence to a correctly prescribed maximal inhaler with inhalant corticosteroids (ICS) and beta2 long-acting agents' treatment. In the presence of certain clinical and laboratory characteristics these patients can be prescribed different biological drugs for SA with anti-IgE or anti-IL5, IL4/IL-13 properties such as, up to now, Benralizumab, Dupilumab, Mepolizumab, Omalizumab (Bagnasco et al., 2021). Correct follow-up of SA patients includes keeping in mind that quality of life (QoL) and productivity of these patients may be affected as increased health care utilization, morbidity and mortality could also occur because of asthma exacerbations (Reddel et al., 2015); furthermore, psychological factors play a primary role in daily asthma management (Baiardini et al., 2015). Among psychological factors suspected to interfere with asthma treatment and still under debate, is alexithymia, i.e., a difficulty in identifying and describing one's own emotions which has been reported to influence the achievement of disease control (Braido, 2013; Myles & Merlo, 2021). In these terms, the study is aimed at presenting domains related to Asthma through a literature mini-review investigating the role of psychological factors in the onset, maintenance and course of the pathology. In order to reach the above-mentioned objective, valuable articles will be included and discussed in line with the reported method.

2. Methods

2.1 Search Strategy and inclusion criteria

The present article consists of a narrative mini-review conducted on the role of alexithymia in the onset, maintenance and gait of chronic conditions. With reference to search engines, PubMed and Google Scholar Scopus databases were used to search English-language articles relating to asthma and alexithymia starting from December 2022. In terms of keywords, "severe asthma" AND "alexithymia" were inserted to search English-language articles. Original papers with available full text were selected and then included in the first step of the study according

to contents and clinical value. Articles not precisely matching with study hypotheses were excluded. Included articles were then reviewed in depth in order to outline recommendations on the clinical management of severe asthma patients with possibly both clinical conditions. Finally, 37 main results were included into two principal domains, respectively related to "Alexithymia and asthma as an inflammatory chronic disease" and "Assessment and management of alexithymia in SA patients". The above-mentioned themes were then analyzed in line with study hypotheses.

3. Results

Table 1. Articles included in the review

Authors	Year	Main findings
Bagby et al.	1994	Cross validation and items selection study for he twenty-item Toronto Alexithymia Scale; three factor structure emerged through factorial analysis, respectively difficulty in identifying and describing feelings, operative thinking (externally oriented thinking).
Baiardini et al.	2021	Evaluation of alexithymia in subjects affected by respiratory allergy; presence and relevance of alexithymia in significant percentage, affecting illness perception, stress dynamics, quality of life, onset and illness progress.
Barbosa et al.	2011	Empirical study on the occurrence of alexithymia in subjects affected by systemic lupus erythematosus; presence of alexithymia and psychological distress influencing subjects' perspective on disease, its course and quality of life in the fields of everyday activities and adaptation.
Barchetta et al.	2021	Presence of alexithymia in healthy subjects capable of generating negative bias on life events and individuals' perspectives. Consistent tendency in devaluating positive events and current possibilities linked to unknown affective dynamics linked to alexithymia.
Beresnevaite	2000	Preliminary study on effectiveness of psychotherapy in reducing alexithymia levels in coronary health disease patients. Indications and evidence of alexithymia levels reduction influencing positively coronary health disease course.

Bermond et al.	2006	Neuropsychological functioning and alexithymia correlates in the field of syndrome, classification of alexithymia types on the basis of psychobiological traits. Neural structures analysis and personality correlates discussion.
Chimenti et al.	2019	Cross sectional study evaluating alexithymia in subjects affected by rheumatoid arthritis and psoriatic arthritis, showing consistent levels of alexithymia and its association with gender and steroid therapy. Suggestion for the implementation of comprehensive management through the inclusion of psychological assessment.
Chiricozzi et al.	2020	Alexithymia studies through its associations and correlations with atopic dermatitis, indicating high scores and significant associations with atopic dermatitis severity, as in the case of borderline alexithymic subjects among clinical group compared with controls.
Craparo et al.	2016	Emotion recognition impairment and alexithymia found in heroin addicted subjects, showing a consistent lack of affective dynamics recognition and alexithymia possible responsibility in the difference between groups (addicts and control).
Erkic et al.	2018	Evidence for deficits in emotional regulation and perception in subjects affected by somatic symptom disorder, presence of emotional recognition deficit together with higher levels of others' emotion disavowal.
Gangemi et al.	2021	Alexithymia presence and relevance in a group of non-clinical subjects demonstrating considerable levels and associations with gender and age as predictors. Indications and implications for future research in the field of the population, considering alexithymia as a possibly unknown but relevant phenomenon.
Honkalampi et al.	2000	High prevalence of alexithymia in the general population, discussion on its association with related dynamics in the onset, course and maintenance of depression and other affective syndromes. Insights on links between alexithymia and depression considering the risk of neglecting emotion recognition abilities.

Innamorati et al.	2015	Evaluation of alexithymia in subjects affected by bronchial asthma and differentiation with subjects experiencing anxiety and depression. The study highlighted the need to consider psychological domains concurring with organic issues in order to provide for proper clinical assistance.
Kaplan et al.	2019	Evaluation of peripheral inflammation in rheumatic disease affects the nervous system, considering psychological domains and possible issue. Consideration of therapies in the required changes and issue solving.
Karabiçak et al.	2021	Study of alexithymia in subjects with inflammatory chronic diseases, particular reference to ankylosing spondylitis. Higher scores in subjects presenting the considered pathological domain, suggestions on the importance of assessment referred to psychological characteristics and syndromes.
Khosravani et al.	2020	Association of alexithymia with physical symptoms, psychosomatic disorders, low empathy and negative affectivity. Significant relations between alexithymic features and physical symptoms, deficits in affective domains, evidence of alexithymia presence in subjects with asthma.
Kleiger & Dirks	1980	Alexithymia, panic-fear scores of MMPI considered in subjects with asthma, highlighting high presence contributing to medical difficulties related to treatment of chronic asthma.
Korkoliakou et al.	2007	Presence of significant psychopathological indexes and alexithymia in patients suffering from psoriasis. Statistically significant scores with reference to somatization, affective disorders and relations between alexithymia, somatization, interpersonal sensitivity, anxiety and phobic anxiety.
Laricchiuta et al.	2015	Neuroimaging studies confirming structural and functional issues of brain areas in subjects with alexithymia, as in the case of emotional awareness; cerebellar activity investigation. Possible functional emotional processing linked to cerebellar involvement and alexithymia implication in altered emotional embodiment processes.
Liotta et al.	2021	Evaluation of possible interference role of alexithymia in omalizumab treatment outcome for subjects suffering from

		severe allergic asthma; no evidence of alexithymia role in the completion of treatment.
Lumley et al.	2005	Relationships among emotional ability through different methods as such interviews, self-report, collateral report and emotion-relevant performance. Differentiation among explicit self, implicit self and explicit other; need for attention with reference to different constructs related to emotional abilities.
Martino et al.	2020	Systematic review suggesting necessary distinctions with reference to alexithymic patients and subjects affected by inflammatory bowel disease not necessarily alexithymic. Despite high presence of alexithymia has been found through the last decades in subjects suffering from psychosomatic conditions, distinctions are necessary. Possible scientific progressions referred to the possibility to realize a significant decrease of IBD subjects' quality of life constituting higher impaired emotion recognition.
Martino et al.,	2021	Relevance of alexithymia in subjects suffering from Hashimoto's thyroiditis, relations with underreported depression state which expression can be mainly highlighted through physical complaints. Intervention based on alexithymia reduction can contribute to clinical treatment of phenomena providing for better elaboration and coping.
Mc Donald et al.	2020	Randomized controlled trial investigating treatable traits in patients suffering from severe asthma, highlighting advantages related to multidimensional assessment and personalised-medicine approach considering subject's complexity.
Nemiah et al.	1976	Theoretical and clinical reflection on alexithymia, providing for understanding of main related phenomena, theoretical evolution and clinical implication considering psychosomatic conditions and related emotional, physical, cognitive and dynamic components.
Papi et al.	2018	Seminar focused on main components, phenomena and characteristics of asthma.
Plaza et al.	2006	Presentation of alexithymia characteristics and impact on subjects with near-fatal asthma. Alexithymia appeared to be

		more consistent in subjects who experienced near-fatal asthma than subjects who have never experienced near-fatal asthma attacks.
Quinto et al.	2021	Study of alexithymia presence in subjects suffering from hidradentitis suppurativa. Alexithymia high and borderline levels were found to be consistent for 44% of patients with a higher prevalence in women. No associations among alexithymia and clinical variables. Significant implications in terms of social and adaptation issues.
Shinan-Altman & Katzav	2020	Alexithymia implications and specific relations with illness representations, coping strategies and well-being in subjects affected by asthma. Higher levels of alexithymia contributing to lower levels subjective well-being.
Sifenos	1996	Study discussing the past and the contemporary progresses on alexithymia, clinical implications and future directions.
Tordeurs et al.	2000	Alexithymia consideration in comparison with variables such as depression and alcoholism. Results showing the central role of alexithymia in psychopathological dynamics.
Upham et al.	2021	Severe Asthma Super-Responder definition issues and implications in the clinical field. Need for implementation of clarity referred to definition and related asthma phenomena.
Van Houtum et al.	2015	Everyday problems interference with chronic illness management and progression. Potential self-management and compliance to treatments reduction due to variables impacting with primary health need of patients.
Vanegas et al.	2020	Cross-sectional study evaluating alexithymia impact and role on patients suffering from asthma. Relevance of mental condition and dynamics on disease control.
Vicario et al.	2021	Neuroscientific paper considering alexithymia and its role with reference to perceptual pseudoneglect. The study supports the hypothesis considering deficits related to right hemisphere.
Vita et al.	2020	Quality of life and its impact on subjects suffering from hyperthyroidism. The study highlights the incidence of psychological domains and phenomena on physical health,

		suggesting both quality of life decrease due to hyperthyroidism and psychological issues typical of the considered condition.
Wriega et al.	2017	Integrative review considering emotional regulation and affective dynamics in subjects with chronic conditions. The result highlighted the need for knowledge implementation with reference to psychological domains related to chronic conditions.

3.1 Alexithymia and asthma as an inflammatory chronic disease

The term alexithymia was coined by Sifneos (1996) and is formed from the Greek 'a' for lack, 'lexis' for words and 'thymos' for emotion (i.e., lack of words for emotions). It refers to a personality construct characterized by difficulty in identifying and describing feelings and distinguishing between feelings and bodily sensations as well as externally oriented thinking, and limited imaginative capacity. Accordingly, individuals with alexithymia may show abnormal emotional awareness and communication and demonstrate little insight into their feelings, symptoms, and motivation (Nemiah et al., 1976). A high rate of alexithymia is reported among patients with psychosomatic disorders and mental health disorders such as anxiety, depression, eating disorders/obesity, addiction, obsessive-compulsive disorder, thus suggesting a strong association between alexithymia and mental illness (APA, 2013; Erkic et al., 2018; Honkalampi et al., 2000; Tordeurs et al., 2000).

Furthermore, recent works have documented a predictive role of alexithymia for cognitive and affective performance in clinical populations. For instance, alexithymia predicts emotion recognition deficits in addiction. The study by Craparo et al. (2016) conducted on thirty-one heroin addicts and thirty-one healthy controls showed a generally lower accuracy and higher Reaction times (RTs) in the recognition of facial expressions of emotions compared to controls. A hierarchical multivariate regression analysis showed that alexithymia might be responsible of the lower ability of people with addiction in emotion detection. Regarding the research on healthy individuals, it was recently documented a spatial attention deficit in alexithymic individuals (Vicario et al., 2021). Two hundred twenty-two participants were asked to complete an online version of the Toronto Alexithymia Scale (TAS-20 scale) and mark the centre of a 10-cm horizontal segment. The results documented a significant rightward shift in the center of the line in participants with borderline and manifest alexithymia as compared with non-alexithymic individuals. Moreover, the higher the TAS-20 score, the greater the rightward shift in the line bisection task. This finding supports the right hemisphere deficit hypothesis in

alexithymia (Bermond et al., 2006) and suggests that visuospatial abnormalities may be an important behavioural correlate of this mental condition. Finally, the study by Barchetta et al. (2021) has found alteration in temporal perspective of people with alexithymia. One hundred and forty-two healthy participants completed an online version of the TAS-20 scale and the Zimbardo Time Perspective Inventory (ZTP-I), which monitors individual differences in time-orientation regarding the past, present, and future. The results show greater attention to past negative aspects in participants whose TAS-20 score was indicating borderline or manifest alexithymia, as compared to non-alexithymic individuals. Moreover, the higher the TAS-20 score, the higher the tendency was to focus on negative aspects of the past and interpret the present fatalistically. These results suggest that difficulties in identifying and describing feelings and emotions are associated with a negative bias for past and present events. The evidence that alexithymia predicts the reproduction variability of sub-second durations of negative affective stimuli is in line with previous neuroimaging studies documenting cerebellar deficits in these individuals (Laricchiuta et al., 2015). As reported in scientific literature alexithymia could also be considered as a possible risk factor for a variety of chronic diseases (Wrienga et al., 2017) and it may interfere with patients' disease management (Van Houtum et al., 2015). Studies carried out on patients with alexithymia suffering from chronic diseases other than SA, have described this disease in association with systemic gastro-intestinal, cardiac or rheumatology diseases such as chronic inflammatory bowel diseases (Martino et al., 2020), ischemic cardiomyopathy (Beresnevaite, 2000) or systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis and psoriatic arthritis (Barbosa et al., 2011; Chimenti et al., 2019; Karabiçak et al., 2021); endocrinological such as thyroid diseases (Martino et al., 2021; Vita et al., 2020) and even chronic inflammatory diseases of the skin have been reported to be characterized by cases of alexithymia as reported in patients with hidradenitis suppurativa, psoriasis and atopic dermatitis (Chiricozzi et al., 2020; Korkoliakou et al., 2017; Quinto et al., 2021). Some of these studies have controlled for the confounding effect of presence of depression and anxiety symptomatology, which did not contribute to this. Psychotherapeutic interventions seem to improve the clinical course of the underlying inflammatory disease and the quality of life of patients; these beneficial effects might be due to the communication between the brain and the immune system as higher levels of inflammation have been reported to be associated with changes in cognitive aspects (Kaplan et al., 2019).

Asthma is an inflammatory chronic disease (Papi et al., 2018) and in real-life studies the prevalence of alexithymia was found to be higher in asthmatic patients compared to the general population, even in high percentages as almost 1 patient out of 5 with asthma (Baiardini et al.,

2011; Gangemi et al., 2021), and alexithymia has been reported more frequently in SA among asthma patients with a percentage of 3 in 10 (Vanegas et al., 2020). Furthermore, Innamorati et al. (2015) reported that in a study among a population of 153 asthma patients, 22% presented SA and 51% of them severe alexithymia.

3.2 Assessment and management of alexithymia in SA patients

A thorough evaluation of the patients in SA outpatient clinics should include the assessment of the presence of alexithymia to plan a personalized disease management (Kleiger & Dirks, 1980; Lumley et al., 2005; Lumley et al., 2007). Notably, the presence of alexithymia in SA patients can be identified by administrating the self-report (Bagby et al., 1994) Toronto Alexithymia Scale (TAS 20), that is comprised of 20 items, rated using a 5-point Likert scale whereby 1= strongly disagree and 5 = strongly agree. There are 5 items that are negatively keyed (items 4, 5, 10, 18 and 19). The total alexithymia score is the sum of responses to all 20 items. The TAS-20 uses cutoff scoring: equal to or less than 51 = non-alexithymia, equal to or greater than 61 = alexithymia. Scores of 52 to 60 = possible alexithymia. In addition to the total score, three sub-scores can be computed all of which measure distinct factors: "difficulty identifying emotions," "difficulty describing emotions," and "externally oriented thinking".

In patients with SA, and therefore who have altered pulmonary function even if under treatment with high dose ICS in addition to long acting beta2 agonists, the administration of the TAS 20 self-report questionnaire is feasible as alexithymia has been reported to interfere with the management of asthma (Khosravani et al., 2020). The need for assessing alexithymia is also justified by the observed correlations with the report of higher alexithymia scores in patients with lower forced expiratory volume in the first second (FEV1) at spirometry, showing worse pulmonary function and disease control; it has been reported that asthma patients with alexithymia have an incomplete control of asthma and an incorrect perception of respiratory signs, such as shortness of breath or dyspnoea as their psychological condition may cause the non-adherence to prescribed asthma medication treatment (Shinan-Altman & Katzav, 2020). Moreover, Liotta et al. (2021) reported that scheduled visits at regular and close intervals over time and personalized treatment plans, could encourage the establishment of a relationship of trust between the doctor and patient and increase the awareness of their illness in SA patients with alexithymia, counteracting the tendency to poor treatment adherence. The introduction in the last two decades of biological treatment for SA has been found to correlate, in alexithymia patients, with a greater control of symptoms, improvement of respiratory function and quality of life as in Liotta's real-life experience where regardless the presence or not of alexithymia, all

patients with SA showed a marked improvement after starting treatment with omalizumab. Furthermore, the SA patients' response to treatments, such as biologics and other add-on therapies, has been reported to correlate not only to treatments' efficacy but also to the patients' total well-being including psychological status (Upham et al., 2021). The incorrect perception of symptoms due to alexithymia, if not investigated in asthmatic patients, may interfere with their capacity to carry on with their activities even if breathless and therefore risk more easily a severe asthma attack (Plaza et al., 2006). Results from a randomized controlled trial on SA patients report that targeting treatable traits through a personalized approach affects them positively; therefore, the suggestion is to follow a multidimensional assessment intervention on pulmonary and extra-pulmonary factors (Mc Donald et al., 2020).

4. Discussion

Asthma severity is reported to be linked to psychological aspects such as subjective perception, coping style and alexithymia (Chugg et al., 2009); the latter is reported to be more present in SA patients even if epidemiologic data about its prevalence in these patients needs further investigations as studies have been carried out only on limited patient populations (Di Giuseppe & Perry, 2021; Selinheimo et al., 2022; Sergi et al., 2023). It has been highlighted asthmatic patients with alexithymia tend to perceive and to live their disease as a cyclical disorder, not a limiting chronic condition (Serrano et al., 2006). As observed in patients affected by other chronic diseases (Conversano et al., 2020; Di Giuseppe et al., 2021; Popoviciu et al., 2022), they have difficulty in recognizing and in reporting bodily sensations as well as emotional feelings and tend to underestimate both physical and emotional components of asthma exacerbations (Chung et al, 2012; Teixeira et al., 2022).

It is possible to hypothesize that SA patients with alexithymia neglect their disease because of their psychologic condition, causing repeated airway epithelium injury because of chronic inflammation; accordingly, it might be plausible that in some SA patients, alexithymia becomes a way to cope with psychological distress resulting from chronic illness, for which assessment results fundamental (Frisone et al., 2021). They become more conscious of their disease only after the improvement of asthma symptoms and QoL induced by the appropriate clinical management and treatment (Vazquez et al., 2010). A severe chronic inflammatory disease such as SA affects not only respiratory biological and functional aspects but often interferes substantially on the social, emotional, family-relational and working life (Hyland et al., 2018). Therefore, we believe that alexithymia, as a peculiar psychological disease different from depression and anxiety (Amore et al., 2013; Myles & Merlo, 2022a, 2022b) should be investigated

in SA patients to ensure a multidisciplinary approach for an optimal management of the disease. The contents of the present review underline that the management of patients with severe asthma in the third millennium must take into consideration, beyond the traditional clinical and objective evaluation of medical intervention, also the impact of the disease on patients' psyche.

Author Contributions

L.R., G.S. and G.M. made significant contribution to the conception and design of the review, to the synthesis and interpretation of data by drafting first and revised versions of the manuscript; L.R. and G.M. provided the acquisition of data; C.M.V., V.C. and M.L. gave significant contribution to draft part of the manuscript; S.G. and G.M. revised the manuscript for intellectual content and gave the final approval of the manuscript to be submitted. All authors contributed to the article and approved the submitted version.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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