European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 3, September-December

Letter to the Editor

CAN ASTHMA AFFECT BRAIN ACTIVITY AND VICE VERSA?

K. Metodiev[1*] and A. Younes[2]

[1] Medical University, Department of Preclinical and Clinical Sciences, Varna, Bulgaria;
[2] Department of Anesthesia and Reanimation, Popoli Civil Hospital, Popoli, Italy.

**Correspondence to*:
Prof. Krassimir Metodiev,
Medical University,
Department of Preclinical and Clinical Sciences,
Varna, Bulgaria.
e-mail: kr.metod@gmail.com

KEYWORDS: *Asthma, CNS, brain, inflammation, chronic disease, neurotransmitter*

INTRODUCTION

Asthma is a recurrent lung disease characterized by respiratory noises, paroxysmal coughing and dyspnea due to hyperactivity with bronchospasm of the tracheobronchial airways that results in difficulty in breathing (1). Asthma is a chronic inflammatory disease of the airways which affects the respiratory system but also has complex interrelationships with the brain through biochemical and neuroimmune pathways (2). Chronic asthma affects neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are essential for mood regulation and cognition.

The onset of the disease can occur at any age but is more frequent between the ages of three to eight years old, with a higher incidence in males. Some risk factors for asthma include low birth weight, living in urban areas, and a family history of asthma or allergies (3). The etiology is multifactorial, from exposure to inhaled or ingested allergens, to infections, smoking, or inhalation of airway irritants. Two-thirds of subjects have allergic diathesis with immune responses mediated by IgE (4). Some studies have highlighted the role of gastroesophageal reflux in adenoid hypertrophy and chronic sinusitis (5).

The symptomatology of asthma is characterized by dyspneic crises with prolonged, labored, and noisy expiration, accompanied by rhonchi, rales, and wheezing. During the attack, the patient may become cyanotic, with sweating, bradycardia, and emission of fluid and bronchial secretion. Critical episodes may be rare or frequent and may involve the heart and pulmonary circulation, which could possibly lead to cardiac failure in the most serious cases (6).

DISCUSSION

Asthma and the central nervous system (CNS) are linked because the CNS regulates the airway muscles and inflammatory responses (7). Stress or anxiety can trigger asthma symptoms or worsen them by affecting airway control and inflammation (8). In fact, CNS activity can influence asthma symptoms, primarily through the interaction between the nervous and respiratory systems. Stress and emotional distress are processed in the CNS and can cause hyperventilation or airway constriction, leading to asthma exacerbation. Stress triggers the release of cortisol and other hormones, worsening airway inflammation (9). The autonomic nervous system regulates airway tone. Overactivation of the parasympathetic nervous system can lead to bronchoconstriction, while sympathetic stimulation may affect airway relaxation (10). Some medications that act on the CNS, such as sedatives or certain opioids, may depress respiratory drive or affect airway responsiveness, potentially triggering symptoms in asthmatic individuals (11).

Received: 28 October, 2024
Accepted: 27 December, 2024

2974-6345 (2024)

CNS-driven hyperventilation can irritate the airways, reduce CO2 levels in the blood, and cause bronchoconstriction. This can mimic or worsen asthma symptoms. Asthma is linked to higher rates of anxiety, depression, and cognitive impairments, likely through the shared inflammatory and neurochemical pathways. Activated Th2 immune responses lead to the elevation of IL-4, IL-5, IL-13, and IgE levels, contributing to lung inflammation and potentially signaling neuroimmune changes (12).

Some activated immune cells, such as mast cells (MCs) in the airways and brain, can release neuropeptides on site, causing airway inflammation, mucus production, and constriction, which worsens asthma symptoms (13). Asthma, MCs, and the brain are interconnected in ways that highlight the intricate link between the immune system, inflammation, and the nervous system (14). MCs are white blood cells involved in allergic reactions and are central to asthma pathophysiology. They reside in tissues like the airway epithelium, where they release histamine, leukotrienes, and cytokines in response to allergens. MCs contribute to bronchoconstriction, airway inflammation, and mucus overproduction, which are all hallmarks of asthma (15). MCs are present in the brain, especially near blood vessels and the meninges and contribute to neuroinflammation by releasing histamine and cytokines that may potentially influence conditions like migraine, multiple sclerosis, and mood disorders (16).

Inflammatory signals from MCs in asthma may influence the blood-brain barrier (BBB), leading to increased neuroinflammation (15). Their overactivation has been implicated in neuropsychiatric conditions such as autism spectrum disorders, anxiety, and post-traumatic stress disorder. Understanding the interrelationship between asthma, MCs, and the brain allows for a better understanding of asthma management by considering not only respiratory symptoms, but also the broader systemic and neurological impacts. The interaction between Th2 immune responses, asthma, and brain function is an important area that still needs to be explored further (17).

T helper cells (CD4+ T cells) are a subset of Th2 cells that orchestrate immune responses against extracellular pathogens. In allergic asthma, Th2 cells are central to allergic responses, driving IgE production and recruitment of other immune cells such as eosinophils and MCs (18). Th2 cells drive IgE production and recruitment of other immune cells. Th2 cells secrete cytokines such as IL-4 that promote IgE class switching in B cells. Inflammatory mediators in asthma, such as IL-1, IL-6, and TNF, might affect cognitive function, mood, and behavior (19). Stress or neural dysfunction can exacerbate asthma by promoting Th2-biased immune responses.

IL-4 and IL-13 are mediators of allergic asthma inflammation and may restrict the brain by promoting systemic inflammation (20). IL-6, although not strictly related to Th2 cells, may have downstream effects on both asthma and neuroinflammation, while IL-33, an alarmin cytokine, may be involved in Th2-mediated responses and neuroimmune interactions.

There's also evidence that asthma can influence brain function, possibly due to low oxygen during severe attacks or chronic inflammation (21). Asthma inflammation can increase the BBB's permeability, allowing systemic inflammatory mediators such as cytokines and chemokines to enter the brain and affect its homeostasis. This may exacerbate neuroinflammation, cognitive decline, or psychiatric disorders. Asthma triggers oxidative stress in both lung and brain tissues due to excessive production of reactive oxygen species (ROS), which can impair mitochondrial function in neurons and contribute to neurodegeneration. Pro-inflammatory cytokines can decrease serotonin availability, contributing to depression or anxiety, which are common comorbidities of asthma.

CONCLUSIONS

Novel therapies focusing on vagal nerve stimulation or antioxidants might benefit asthma and brain dysfunction. Anti-inflammatory drugs including corticosteroids and biologics targeting cytokine mediators might also indirectly improve brain health. Anti-IgE treatments such as omalizumab (a monoclonal antibody used during the treatment of severe-to-moderate persistent asthma in patients who cannot control symptoms with corticosteroids) reduce the symptoms of allergic asthma. Cytokine inhibitors are now also used in severe asthma. In addition, addressing stress and improving mental health can modulate immune responses and potentially improve asthma outcomes.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. Drazen JM, ed. *New England Journal of Medicine*. 2017;377(10):965-976. doi:https://doi.org/10.1056/nejmra1608969

2. Busse WW, Lemanske RF. Asthma. Mackay IR, Rosen FS, eds. *New England Journal of Medicine*. 2001;344(5):350-362. doi:https://doi.org/10.1056/nejm200102013440507
3. Mims JW. Asthma: Definitions and Pathophysiology. *International Forum of Allergy & Rhinology*. 2015;5(S1):S2-S6. doi:https://doi.org/10.1002/alr.21609
4. Bousquet J, Anto JM, Wickman M, et al. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis. *Allergy*. 2015;70(9):1062-1078. doi:https://doi.org/10.1111/all.12637
5. Baumann I, Yılmaz Topçuoğlu MS, Hackenberg S, Sommerburg O. Pädiatrische chronische Rhinosinusitis. *HNO*. 2023;72(4):250-256. doi:https://doi.org/10.1007/s00106-023-01405-8
6. Folmsbee SS, Gottardi CJ. Cardiomyocytes of the Heart and Pulmonary Veins: Novel Contributors to Asthma? *American Journal of Respiratory Cell and Molecular Biology*. 2017;57(5):512-518. doi:https://doi.org/10.1165/rcmb.2016-0261tr
7. Kline JN, Rose RM. Central nervous system influences in asthma. *Advances in Experimental Medicine and Biology*. 2014;795:309-319. doi:https://doi.org/10.1007/978-1-4614-8603-9_19
8. Gans MD, Gavrilova T. Understanding the immunology of asthma: Pathophysiology, biomarkers, and treatments for asthma endotypes. *Paediatric Respiratory Reviews*. 2020;36(36):118-127. doi:https://doi.org/10.1016/j.prrv.2019.08.002
9. Powrie RO, Larson L, Miller M. Managing Asthma in Expectant Mothers. *Treatments in Respiratory Medicine*. 2006;5(1):1-10. doi:https://doi.org/10.2165/00151829-200605010-00001
10. Rodriguez Bauza DE, Silveyra P. Asthma, atopy, and exercise: Sex differences in exercise-induced bronchoconstriction. *Experimental Biology and Medicine*. 2021;246(12):1400-1409. doi:https://doi.org/10.1177/15353702211003858
11. Joseph KS. Asthma Mortality and Antipsychotic or Sedative Use What is the Link? *Drug Safety*. 1997;16(6):351-354. doi:https://doi.org/10.2165/00002018-199716060-00001
12. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Seminars in Immunology*. 2019;46(101333):101333. doi:https://doi.org/10.1016/j.smim.2019.101333
13. Galli SJ. Mast Cells and KIT as Potential Therapeutic Targets in Severe Asthma. *New England Journal of Medicine*. 2017;376(20):1983-1984. doi:https://doi.org/10.1056/nejme1702653
14. Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A. The role of mast cells in migraine pathophysiology. *Brain Research Reviews*. 2005;49(1):65-76. doi:https://doi.org/10.1016/j.brainresrev.2004.11.006
15. Theoharides TC. Ways to Address Perinatal Mast Cell Activation and Focal Brain Inflammation, including Response to SARS-CoV-2, in Autism Spectrum Disorder. *Journal of Personalized Medicine*. 2021;11(9):860. doi:https://doi.org/10.3390/jpm11090860
16. Kritas SK, Gallenga CE, Ovidio CD, et al. Impact of mold on mast cell-cytokine immune response. *J Biol Regul Homeost Agents*. 2018;32(4):763-768.
17. Fernández-Gallego N, Castillo-González R, Méndez-Barbero N, et al. The impact of type 2 immunity and allergic diseases in atherosclerosis. *Allergy*. 2022;77(11):3249-3266. doi:https://doi.org/10.1111/all.15426
18. Komlósi ZI, van de Veen W, Kovács N, et al. Cellular and molecular mechanisms of allergic asthma. *Molecular Aspects of Medicine*. 2021;85:100995. doi:https://doi.org/10.1016/j.mam.2021.100995
19. Yang Z, Wu CAM, Targ S, Allen CDC. IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. *The Journal of Experimental Medicine*. 2020;217(5). doi:https://doi.org/10.1084/jem.20190472
20. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188-1204. doi:https://doi.org/10.1111/all.14151
21. Hochgerner M, Sturm EM, Schnoegl D, Kwapiszewska G, Olschewski H, Marsh LM. Low oxygen levels decrease adaptive immune responses and ameliorate experimental asthma in mice. *Allergy*. 2021;77(3):870-882. doi:https://doi.org/10.1111/all.15020