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Clearing Up the Fog: Insights Into Brain Fog Experienced by Patients With Hypothyroidism

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Between 4.6% and 9.5% of the population in the United States is affected by hypothyroidism.^{1,2} The standard of care for the treatment of hypothyroidism is daily thyroid hormone replacement at doses that render the patient euthyroid. Levothyroxine, the most common form of thyroid hormone replacement, is one of the most frequently prescribed medications in the United States.^{3,4} However, there remains a subset of patients on thyroid hormone replacement who exhibit persistent nonspecific symptoms, sometimes even in the setting of a normal serum thyroid-stimulating hormone level. For example, some of these patients exhibit brain fog, fatigue, weight gain, and psychological symptoms such as depressed mood.^{5–8} Dissatisfaction with their current thyroid hormone replacement therapy is also a common complaint among some patients with hypothyroidism.^{7,9}

Despite the impact of nonspecific symptoms like brain fog on some patients' quality of life, brain fog in patients with hypothyroidism and the effective strategies to manage it are poorly characterized in the thyroid literature. The cause of brain fog in patients with hypothyroidism is likely multifactorial, including inadequate treatment with thyroid hormone replacement and the presence of comorbid conditions. In a cross-sectional study of adults with hypothyroidism in the United States using data from the National Health and Nutrition Examination Survey, 23.2% of the cohort was found to have untreated hypothyroidism.¹⁰ The authors of this study also identified sociodemographic disparities in the treatment of hypothyroidism, with inadequate treatment associated with Hispanic race; and lack of treatment with thyroid hormone associated with male sex, age younger than 45 years, and lack of routine health care access.¹⁰ Similarly, male sex and younger age were found to be associated with undertreatment in a retrospective study of patients receiving treatment with levothyroxine in the United Kingdom.¹¹ The clinical challenges

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of treating patients with hypothyroidism and brain fog are also likely related to the nonspecific nature of this condition, which has been described in patients with thyroid and nonthyroid conditions, including menopause, celiac disease, and most recently, the COVID-19 syndrome.¹²⁻¹⁴ Thus, research that explores how the term “brain fog” is used by patients and which factors mitigate this condition is critically necessary for interventions focused on addressing brain fog, thereby, ultimately improving quality of life for patients with hypothyroidism.

In this context, the population-based survey study by Ettleson et al¹⁵ entitled “Brain Fog in Hypothyroidism: Understanding the Patient’s Perspective,” provides important new evidence to guide clinicians’ approach to address brain fog in patients with hypothyroidism. The authors surveyed 5170 individuals using an online survey instrument adapted from the thyroid-related patient-reported outcome questionnaire, which measures a range of aspects of quality of life relevant to patients with benign thyroid diseases.¹⁶ The survey included questions on self-reported symptoms associated with brain fog while on treatment for hypothyroidism. The majority of the participants reported experiencing brain fog at least “frequently” and that it lasted all day (79.2% and 56.4%, respectively). In addition, almost half of the participants reported experiencing brain fog predating their diagnosis of hypothyroidism (46.6%). Overall, >95% of the patients associated brain fog with symptoms of low energy/fatigue, forgetfulness, sleepiness, and difficulty focusing. Thus, among patients with hypothyroidism, “brain fog” was a term used to broadly describe a multisystem condition encompassing both cognitive and physical symptoms. Furthermore, participants reported that it was common for these brain fog symptoms to negatively impact their quality of life.

Unique to this study, Ettleson et al go beyond just characterizing brain fog to identifying potential strategies to mitigate this multisystem condition from the perspective of patients with hypothyroidism. The most common alleviating factors for brain fog identified were more rest, which was reported by 51.7% of participants, followed by the adjustment of thyroid hormone replacement (28.3%) and more exercise (10.4%). Counseling patients with hypothyroidism who complain of brain fog has traditionally been challenging for clinicians, as there are limited data on effective treatment options. Thus, the identification of specific lifestyle modifications that may alleviate brain fog is certainly helpful to guide clinicians treating patients with hypothyroidism and brain fog, especially in the setting of normal serum thyroid-stimulating hormone levels.

The strengths of the study include the large sample size, the use of a questionnaire adapted from a validated instrument, and the unique and clinically relevant research question. The limitations of the study include selection bias, as participants were recruited from hypothyroid support groups; the survey instrument being only available online and in English; and recall bias. Second, the response rate of the survey could not be calculated based on the survey methods used. Third, information on the patients’ thyroid function (ie, thyroid-stimulating hormone, free triiodothyronine, or free thyroxine levels) and the presence of comorbid conditions (ie, depression, sleep apnea), which may contribute to symptoms associated with brain fog, was unavailable for this study. There is also a lack of granular data on the experience of patients with brain fog predating their hypothyroidism

diagnosis, including how thyroid hormone replacement initiation altered the brain fog symptoms, if at all.

Although limitations exist, this study highlights patients' experiences with brain fog, a critically important but understudied area in the thyroid literature, and offers evidence for clinicians on the treatment of this poorly understood multisymptom condition. The study findings suggest that, for a subset of patients with hypothyroidism, a multipronged approach may be required to achieve a euthyroid state and reduce the symptom severity. Future studies should focus on further understanding the impact of lifestyle and behavioral modifications on improving symptoms such as brain fog in patients with hypothyroidism while maintaining biochemical euthyroidism.

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