

Mental Health Disorders and Hyperthyroidism in the Pediatric Population

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Hyperthyroidism (particularly Graves' disease) affects people of all ages, with symptomatology including restlessness and inability to focus, anxiety, weight loss, tachycardia, heat intolerance, diaphoresis, and diarrhea. The conventional wisdom is that symptoms resolve once the hyperthyroidism is adequately treated. However, authors of some reports suggest that with respect to mental health, this may not be the case. In this issue, Zader et al¹ investigate this question and conclude that children with hyperthyroidism have a higher prevalence of attention-deficit/hyperactivity disorder (ADHD), adjustment disorder, anxiety, bipolar disorder, depression, and suicidality.

The authors used the Military Health System Data Repository to identify children aged 10 to 18 years in the military system for ≥ 1 month who had International Classification of Diseases, Ninth Revision or International Classification of Diseases, 10th Revision codes for hyperthyroidism and the aforementioned mental health conditions. The Military Health System Data Repository included >2.5 million children, with a total of nearly 2500 children with hyperthyroidism during a 9-year interval. Compared with children without hyperthyroidism, the prevalence ratios of mental health conditions in those with hyperthyroidism ranged from 1.7 (ADHD) to 4.9 (bipolar disorder). In $>40\%$ of cases, the mental health diagnosis antedated the

hyperthyroidism by > 90 days, with ADHD being diagnosed before hyperthyroidism in 68.3% of cases. Suicidality was nearly fivefold more likely in those with hyperthyroidism than in those without. The overall incidence of mental health conditions in military children was commensurate with reported population norms.

There is a paucity of information regarding chronic mental health conditions and hyperthyroidism. Because the pediatric literature consists mainly of case reports, we look to studies in adults. Thomsen et al² compared $>183\,000$ hospitalized people aged ≥ 15 years with hyperthyroidism versus nontoxic goiter versus osteoarthritis and found that those with hyperthyroidism had a significantly greater risk of readmission with depression or bipolar disorder compared with the control groups. Similar results were obtained in a Taiwanese study of two 21 000-patient matched cohorts revealing a risk ratio of >2 for bipolar disorder in those with hyperthyroidism, with autoimmune disease being 1 of the predictors in univariate analysis.³ Authors of a more recent Danish study specifically compared anxiety and depression in those with Graves' disease versus toxic nodules and showed that the incidence of depression and anxiety was significantly higher in those with Graves' disease, irrespective of thyroid function tests and antibody level.⁴



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The mechanisms behind this association are still under investigation, although there are some hints, such as the studies above suggesting a greater incidence with autoimmune hyperthyroidism. Additionally, a British cohort study revealed a bidirectional relationship with depression and autoimmunity, although the authors did not separate out different autoimmune diseases.⁵ A meta-analysis of 19 studies and >36 000 patients did associate depression and anxiety with autoimmune thyroiditis, lending evidence to an association between autoimmune thyroid hormone dysregulation and mental health outcomes.⁶ With respect to bipolar disorder, hyperthyroidism and bipolar disorder are comorbid, although occurrence of the 2 together is relatively rare.⁷ A potential connection is that lithium is associated with hyperthyroidism, although hypothyroid effects are much more common.⁷ There are additional potential mechanistic possibilities in that tyrosine is a precursor for both thyroid hormones and norepinephrine and dopamine, both of which are dysregulated in mental illness.^{8,9} Thyroid hormone receptors are widely distributed in the brain, and the thyroid has enzymes for γ -aminobutyric acid synthesis and degradation, indicating likely physiologic overlap between the 2 systems.⁷ There is also a hypothesis that depression is associated with local brain hypothyroidism that may not be evident systemically.⁸ At present, there are only clues as to the mechanisms behind the association, and it will be interesting to see additional research in this area.

The study by Zader et al¹ is important in that it is the first to reveal a strong association between mental health conditions and hyperthyroidism in the pediatric population in a large sample size. The results are consistent with the adult literature. Limitations of the study include a transient population and the absence of demographic description, thus limiting the potential translatability. However, the reported incidence of mental health conditions in the military population is similar to that in the general population, and the racial and ethnic diversity is likely similar. Given their study design, the diagnosis could not be verified, and the actual thyroid hormone levels as well as treatments (for hyperthyroidism or mental health conditions) are unknown, leading to possible confounders. Additionally, the data on the relative time courses are scant. Despite these limitations, the authors appropriately raise the important point that the American Thyroid Association guidelines do not address the mental health aspects of the disease, in particular the apparent increased risk for suicidality.¹⁰ They support the need for this aspect to be addressed and for additional investigations to better understand risk factors, pathophysiology, and effective treatment modalities.

ABBREVIATION

ADHD: attention-deficit/
hyperactivity disorder

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