

# Anorexia and Autoimmunity: Challenging the Etiologic Constructs of Disordered Eating

Rebecca E. Hommer, MD, Susan E. Swedo, MD

Eating disorders, particularly anorexia and bulimia nervosa, have traditionally been viewed as arising from a conglomeration of psychological, biological, and sociocultural factors.<sup>1</sup> Family and individual psychotherapy are mainstays of treatment, but not all youth respond to these interventions, leaving patients at increased risk of death from suicide or medical consequences of their disordered eating.<sup>1,2</sup> The need for new and more effective treatments has prompted investigations into the role of immune function in anorexia and bulimia. Similar lines of research have proven fruitful for a variety of mood, psychotic, and neurodevelopmental disorders, which have been linked to immune dysfunction via epidemiologic, genetic, and immunologic studies.<sup>3</sup>

A few studies in adult populations have found that eating disorders and autoimmune disease each confer an increased risk for the other disorder, but the role that immune disturbances might play in the onset of eating disorders among youth remains largely unexplored.<sup>4,5</sup> In “Eating Disorders, Autoimmune, and Autoinflammatory Disease,” Zerwas et al<sup>6</sup> address these gaps in the literature by documenting bidirectional associations between autoimmune and/or autoinflammatory diseases and eating disorders in a large, population-based cohort study of ~1 million Danish children and adolescents. These associations are present in both sexes but appear to be stronger for boys than girls, perhaps reflecting the relative rarity of eating

disorders among adolescent boys.<sup>6</sup> A family history of autoimmune and/or autoinflammatory disorders in a first-degree relative also increased the risk of eating disorders among the youth.<sup>6</sup>

The Zerwas et al<sup>6</sup> study is the first to demonstrate a bidirectional and multigenerational association between eating disorders and diseases of both innate and humoral immunity in a large, population-based cohort of children and adolescents. These results provide important context for the small number of reports that have linked disordered eating and pediatric autoimmune and/or autoinflammatory diseases. The first such cases were reported nearly a century ago by Hammes<sup>7</sup> and described a cohort of children with Sydenham chorea, the neurologic manifestation of acute rheumatic fever. Food refusal was common, and several children required tube feedings because of “psychotic worries” that their food was “doped,” poisoned, or otherwise contaminated.<sup>7</sup> Seven decades later, investigators at the National Institute of Mental Health described restricted food intake in a number of their patients with Sydenham chorea, including 2 boys who developed distorted body image and engaged in excessive exercise.<sup>8</sup>

In 2000, Sokol<sup>9</sup> described the clinical course of 4 children admitted to an inpatient eating disorders treatment facility who had a history of streptococcal infection preceding the onset of anorexia; all 4 experienced significant improvement in symptoms after antibiotics were added to the



Section on Behavioral Pediatrics, National Institute of Mental Health, Bethesda, Maryland

Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

**DOI:** <https://doi.org/10.1542/peds.2017-3060>

Accepted for publication Sep 12, 2017

Address correspondence to Rebecca E. Hommer, MD, NIH/NIMH/SBP, 10 Center Dr, MSC 1255, Bethesda, MD 20892-1255. E-mail: [rebecca.hommer@nih.gov](mailto:rebecca.hommer@nih.gov)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Supported in part by the Intramural Research Program of the National Institute of Mental Health (ZIAMH002666). Funded by the National Institutes of Health (NIH).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**COMPANION PAPER:** A companion to this article can be found online at [www.pediatrics.org/cgi/doi/10.1542/peds.2016-2089](http://www.pediatrics.org/cgi/doi/10.1542/peds.2016-2089).

**To cite:** Hommer RE and Swedo SE. Anorexia and Autoimmunity: Challenging the Etiologic Constructs of Disordered Eating. *Pediatrics*. 2017; 140(6):e20173060

typical regimen of care. These children were given the diagnosis of acute-onset anorexia in the setting of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). PANDAS, which is typically characterized by the sudden onset of severe obsessive-compulsive symptoms after a Group A streptococcal infection, is thought to be a postinfectious neuroinflammatory disorder with similar pathophysiology to Sydenham chorea. Symptoms are thought to reflect a misdirected immune response in a genetically vulnerable child in which the immune system directs its response against host proteins as well as Group A streptococcal epitopes.<sup>10</sup> A follow-up study of 20 children with PANDAS–anorexia nervosa type suggested that D8/17–positive B lymphocytes may be a marker for the disorder, supporting the notion that the sudden onset of anorexia may, for some children, represent an immune-mediated process.<sup>11</sup>

Meanwhile, interest in identifying other environmental triggers for childhood neuropsychiatric disorders has continued to grow. Diagnostic criteria limit the cohort to those with the abrupt, dramatic onset of obsessive compulsive disorder or severely restricted food intake in conjunction with a constellation of other mood, behavioral, and sensorimotor symptoms.<sup>12</sup> These patients are grouped together under the umbrella of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), which posits a number of potential etiologies, including a direct causal relationship between immune dysfunction and disordered eating.<sup>12</sup> In a recent case review, Toufexis, et al<sup>13</sup> describe this phenomenon in 29 children with PANS, noting their young age (mean 9 years; range 5–12 years), male predominance (a characteristic of PANS and PANDAS more generally and, interestingly,

in keeping with the stronger relationship between immune dysfunction and eating disorders in the boys observed in Zerwas et al's<sup>6</sup> study), and the similarities between PANS symptoms and those of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnosis of avoidant/restrictive food intake disorder.

In summary, Zerwas, et al<sup>6</sup> make a significant contribution to the growing body of literature supporting an association between immune system dysfunction and eating disorders. Further research is needed to delineate the nature of this shared pathophysiology and the extent to which immune-mediated interventions may play a role in treatment. Clinicians are encouraged to consider the possibility that patients with eating disorders may have underlying autoimmune or autoinflammatory conditions. This is particularly important for young boys who present with the abrupt onset of food or fluid intake restrictions and accompanying cognitive, emotional, behavioral, or somatic symptoms. Conversely, we must also remain vigilant about the development of eating disorders among patients with autoimmune or autoinflammatory disorders.

#### ABBREVIATIONS

PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

PANS: Pediatric Acute-onset Neuropsychiatric Syndrome

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DOI: 10.1542/peds.2017-3060 originally published online November 9, 2017;

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