

## The Role of Allergic Diseases in Common Pediatric Mental Health Disorders – A brief literature review

Tonny Tanus,<sup>1</sup> Sunny Wangko,<sup>2</sup> Sally M. Tanus<sup>3</sup>

<sup>1</sup>Kern Allergy Medical Clinic, Clinical Instructor, Bakersfield, CA

<sup>2</sup>Indonesian Anatomists Association

<sup>3</sup>Department of Counseling, Wellspring, Bakersfield, CA

Email: DrTTanus@UCLA.edu

**Abstrak:** Peningkatan risiko masalah kejiwaan akibat kondisi alergi berdampak besar terhadap implikasi klinis. Peran dan parahnya kondisi alergi perlu dipertimbangkan pada anak dengan ansietas atau depresi. Dikatakan bahwa pengobatan alergi dapat mencegah bahkan memperbaiki masalah kejiwaan yang terjadi namun penatalaksanaan alergi secara terpadu dapat membantu mengatasi depresi dan ansietas. Antihistamin generasi pertama telah dikenal berpengaruh terhadap kesehatan mental. Adanya hubungan erat antara alergi dan kesehatan mental menyebabkan steroid topikal dan bila diperlukan antihistamin generasi kedua layak menjadi pilihan. Rentannya pasien dengan alergi terhadap risiko masalah kejiwaan mendorong para klinisi agar lebih memahami bahwa pengobatan psikiatri juga dibutuhkan pada penatalaksanaan alergi dan rekomendasi terapi yang sesuai.

**Kata kunci:** alergi, kesehatan jiwa

**Abstract:** Increased risk of mental health problems brought by allergic conditions has substantial clinical implications. The role and the severity of allergic conditions need to be assessed when children present with anxiety or depression. Although many have proposed that treatment of allergies may prevent and help mental health diseases and definitely deserve further consideration and studies in real practice, concurrent allergy management has been found to help relieving depression and anxiety. First generation antihistamines are well known for their mental health effect. In light of the strong link between allergies and mental health, topical steroids and if needed, the second generation antihistamines would be the preferred choice. Awareness of this link that patients with allergic disorders have higher risk of psychiatric diseases would hopefully make clinicians be more aware that psychiatric treatments will need to include assessment of allergy and recommendation of appropriate therapy.

**Keywords:** allergy, mental health

### Introduction

Allergic diseases, a group of immune mediated disorders, manifest in many diverse organs especially upper and lower airways, skin, and gastrointestinal tracts. The mechanism of allergic response is way more complicated than what was thought to be IgE production and simply linking the two mast cells with IgE and hence de-

granulating those cells releasing histamines. From the initial allergen contact, both B and T cells responded amongst the myriad of affected cells including eosinophils, dendritic and epithelial cells. Various cytokines and cytokine receptors are involved in mediating this complex reaction.

The prevalence of pediatric allergic conditions has continued to rise and asthma

now is the most common non-infectious pediatric condition worldwide.<sup>1</sup> Overall allergy disorder affects approximately 10-20% of all children depending on geographic area. Even if only limiting the discussion to the three A's of allergy: allergic rhinosinusitis, asthma, and atopic dermatitis (eczema), the burden of the disease is tremendous. Children with these conditions are high utilizer of medications and planned medical office visits as well as unplanned health care in the emergency rooms and urgent care centers. Direct comorbidities of these conditions such as sinus and ear infections, secondary skin infections in eczema, bronchitis in asthma, and systemic steroids use in the 3 A's are only part of the very costly equation. The more difficult burden to measure is the compounded effect of missed schools and effect on their education, missed work of parents and caretakers, missed sports, arts and various daily activities as well as the effect on their mental health.

Asthma the chronic allergic disease with periodic exacerbations has been studied extensively. As mentioned, it has been shown to cause suffering in children because of the many emergency room visits and hospitalizations and even death. But as is true with the other allergic conditions, the extra medical burdens with school absenteeism and loss of parental productivities are considerable and very expensive. The earlier age of asthma onset, especially if diagnosed before 6 years of age leads to persistent asthma in childhood.<sup>2</sup> The effects of these relatively common and chronic long term pediatric conditions of allergy and asthma on mental health of children will be discussed.

### **Mental Health Issues**

Mental health issues are quite prevalent worldwide, especially the disorders of anxiety and depression. As the children age, the prevalent doubles between school aged children compared to preschoolers and more than quadruple in adolescents. Diagnosis is often difficult without the help of mental health profes-

sionals because often the assumption that the children are going through a "phase" rather than suffering from a mental health disease. Physical clues though non-specific can be helpful such as sleep deprivation or too much sleep, loss of appetite, difficulties with concentrating on specific tasks or lack of motivation and even actual physical illnesses such as stomach pains and headaches. Treatment with medication such as antidepressant is quite helpful, but when combined with psychotherapy and counseling, the efficacy usually exceeds 70%.<sup>3,4</sup>

### **Allergies and Pediatric Mental Health**

Allergic inflammation is caused by IgE mediated early and late phase hypersensitivity reactions which can affect multiple organs; the most common is the effect on the nasal mucosa causing allergic rhinitis (AR). Typical symptoms include nasal congestion, rhinorrhea, itching, and sneezing, and often accompanied by eye symptoms such as irritated red, itchy, and watery eyes of allergic conjunctivitis (AC).

The role of allergies in asthma is well established; more than 90% of children with asthma have underlying allergies.<sup>5</sup> In Asian studies approximately half of pediatric asthma patients were also diagnosed with allergic rhinitis.<sup>6</sup> Severe uncontrolled asthma afflicts 2-3% of United States asthma population; similarly 1-3% of Japanese children with physician diagnosed asthma are treated with oral corticosteroids.<sup>1,7</sup> But even non-severe asthmatic children have many other ongoing chronic comorbidities such as obesity, gastrointestinal disorders, and psychiatric diseases, hence the Global Initiative for Asthma (GINA) recommendation of treating all active identified comorbidities.

Food allergy is another allergic disorder that is increasing in its incidence without any definitive reason.<sup>8</sup> Interestingly, compared to other allergic disorders, food allergy is the least associated with mental health. Large review conducted in accordance with the Cochrane Handbook for Systematic Reviews involving approxi-

mately 60000 children showed that while children with Attention Deficit Hyperactivity Disorder (ADHD) were twice as likely to have asthma and 59% of greater odds of having allergic rhinitis, it showed very minimal effect on atopic dermatitis and no effect of having food allergy.<sup>9</sup> Other reviews including cross sectional and longitudinal population studies though supported the idea that major depression is associated with increased risk of allergic diseases except for food allergies.<sup>10</sup>

Other allergy related common conditions that have inconclusive relationships with mental disorders are atopic dermatitis and chronic rhinosinusitis (CRS). Some preliminary studies showed some association of chronic sinusitis and psychological disorders, and more recent analysis did show common occurrence of mental health disease such as depression in CRS upward of more than 20% of prevalence of depression. But unlike previous studies, it showed no significant difference of psychological disorders between CRS patients and control group.<sup>11</sup> In atopic dermatitis (AD) studies, the association of mental health diseases and AD was still inconclusive, some showed positive correlation while others showed either negative or very minimal, and not statistically significant difference.<sup>9,12</sup>

In contrast, multiple reviews have consistently showed bidirectional effect of mental disorders in allergic rhinitis and asthma.<sup>10,12,13</sup> Although it is well established that mental disorders do affect allergic rhinitis and asthma, in this review, we will primarily concentrate on the secondary effect of allergic conditions of AR and asthma in depression and anxiety disorders.

### **Allergy Effect on Mental Health**

The evidence on allergies affecting mental disease is emergent but becoming more definitive as recent large reviews were done. Years ago when only cross sectional studies and self-reported data are available, the initial thought was that the link was methodological bias.<sup>14</sup> More

longitudinal studies were performed in Western countries as well as Asia beginning in the 1990's showed the evidence to the contrary. Over 300 adolescents participated in a United States (US) community, longitudinal study with mental health assessment at 7, 9, 11, and 13 years of age, showed a "dose-effect" that lifetime history of asthma and AR associated with anxiety.<sup>12</sup>

A later study of 762 children incorporated skin testing at ages 1, 2, 3, 4, and 7 years for most of the cohort (562 children). Elevated anxiety scores were found in 21% of AR patients, 24% of allergic persistent wheezing, and 27% of multiple allergic diseases, a 2.2 odd ratio.<sup>15</sup> AR was also found to be highly associated with depression, elevated depression scores were found in 19% of AR, 22% of allergic persistent wheezing, and 27% of AR plus another allergic disease. The AR alone had an odd ratio of 3.2 for elevated depression score.

A larger more recent survey type of study which included teenagers as well as adults in US, showed similar findings. Lifetime allergy was significantly associated with 43% of greater odds of anxiety and 28% of greater odds of having mood disorders.<sup>16</sup> Similar population based study in Asia has shown basically identical findings.<sup>13</sup> International review of existing evidence within the last 2 decades involving over 2000 records and 31 full text articles in adolescent patients concluded that adolescents with AR were more likely to be emotionally unstable, with 57.1% of those with severe AR had emotional instability. Compared to controls, adolescents with AR had higher statistically significant rate of anxiety and depression.<sup>17</sup> The bottom line conclusion from these recent large studies is that having AR and asthma significantly increase childrens' risk of anxiety and depression.

### **Mechanism of Allergic Effect on Mental Disorders**

The research on the etiology of allergic effect on mental disorders is severely lacking, especially in pediatric population.

One hypothesis is the effect on sleep hence the deleterious effect on physical and mental well-being.<sup>18</sup> Qualitative study among Spanish adolescents with AR showed sleep difficulties as consequences of their condition.<sup>19</sup> Although this finding has been recently corroborated, direct effect of allergies causing sleeping disorders and in turn causing anxiety and depression was not found.<sup>17</sup>

Evidence of immune system abnormalities in depression and other mental disorders though quite sparse, has also been emerging. Cellular immune reactions with cytokine productions have been shown in depressive disorder. Post-traumatic stress disorder studies showed increase of inflammatory cytokines such as IL-1, IL-6, and TNF-alpha.<sup>20</sup> These increased interleukins are negatively correlated with cortico-striatal connections. In turn, the decreased connectivity between striatum and prefrontal cortex is found to be associated with increased anhedonia.<sup>21</sup>

The other set of emerging evidence relates to inflammatory nature of allergic reactions. Studies in mice showed significant effect on the hypothalamic-pituitary-adrenal axis (HPA), stimulating the release of cortisol hence modifying the serotonin release leading to mood disorder.<sup>15</sup> The inflammatory cascade also caused release of compounds including cytokines that reduce the reduction of monoamine synthesis therefore increasing the synaptic reuptake of monoamines and its neurotoxic effect. These then caused the depressive symptoms.<sup>22</sup>

The main treatments for allergic rhinitis and asthma have been established using international guide lines for years. Both required first line topical or inhaled steroids either nasally for rhinitis and inhalation orally for asthma. The argument for second, third line and non-steroidals such as various biologics for asthma and recently approved anti-IL 4/13 for nasal polyps/ sinusitis is beyond the scope of this review. However one important related issue is the over use of first generation antihistamines despite the known guideline

against it. First generation antihistamines are well known for their mental health effect increasing sedation, fatigue and impacting the psychomotor abilities. In light of the strong link between allergies and mental health, topical steroids and if needed, the second generation antihistamines would be the preferred choice.<sup>23</sup> Awareness of this link that patients with allergic disorders have higher risk of psychiatric diseases would hopefully make clinicians be more aware that psychiatric treatments will need to include assessment of allergy and recommendation of appropriate therapy.

Although many have proposed that treatment of allergies may prevent and help mental health diseases and definitely deserve further consideration and studies,<sup>13,15</sup> in real practice, concurrent allergy management has been found to help relieving depression and anxiety.<sup>24</sup>

### **Conclusion**

The increased risk of mental health problems brought by allergic conditions has substantial clinical implications. Though more detailed cause and effect mechanism of action needs to be further studied, it is clear that the role and the severity of allergic conditions need to be assessed when children present with anxiety or depression. Although many have proposed that treatment of allergies may prevent and help mental health diseases and definitely deserve further consideration and studies, in real practice, concurrent allergy management has been found to help relieving depression and anxiety.

### **Conflict of interest**

The authors affirm no conflict of interest in this study.

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