

Under-recognized Effects of Allergic Disorders on Neuropsychiatric Symptoms, in Subjects with Limited Expressive Language

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Abstract

Diagnosis of allergic diseases are based on detailed clinical history and careful physical examinations supported by skin test (ST) reactivity and/or presence of allergen specific IgE in the serum for IgE-mediated allergy. Clinicians tend to focus on clinical manifestations that occur in the organs affected directly by allergen exposure. However, many epidemiological studies support a positive association between neuropsychiatric symptoms and allergic diseases, although in most epidemiological studies, allergy diagnoses are based on self-reported survey results and/or billing codes.

With current diagnostic tools heavily relying on clinical history, individuals with limited expressive language (LEL) imposes a significant challenge for practicing clinicians. LEL subjects also often exhibit neuropsychiatric symptoms associated with their primary medical conditions. In such subjects, it is often very difficult to differentiate neuropsychiatric symptoms associated with pain and discomfort caused by allergic diseases from those caused by their primary medical conditions. In addition, lack of appreciation of their allergic conditions by the care-givers may further frustrate LEL subjects, rendering worsening their behavioral symptoms.

This review was formulated to address the association between neuropsychiatric symptoms and allergic disorders, emphasizing the need for the special attention required when evaluating LEL subjects for allergic diseases. Since many allergic diseases are relatively easily treatable with benign medications, clinicians need to carefully evaluate and treat common allergy conditions in LEL subjects, especially prior to treating them with neurotropic medications, which likely cause more undesirable side effects.

Keywords: Allergy; Neuropsychiatric symptoms; Limited expressive language; Intellectual and developmental disabilities

Abbreviations

AD: Atopic Dermatitis; ADHD: Attention Deficit Hyperactivity Disorder; A/I: Allergy/immunology; aOR: Adjusted Odd Ratio; AR: Allergic Rhinitis; ASD: Autism Spectrum Disorder; CI: Confidence Interval; CP: Cerebral Palsy; CRS: Chronic Rhinosinusitis; DSM-5: The Diagnostic and Statistical Manual of mental disorders, 5th edition; IDD: Intellectual and Developmental Disorders; IgE: Immunoglobulin E; LEL: Limited Expressive Language; MIA: Maternal Immune Activation; OCD: Obsessive Compulsive Disorder; OR: Odd Ratio; OTC: Over the Counter; PD: Panic Disorder; QOL: Quality of Life; RR: Relative Risk; ST: Skin Testing; WHO: World Health Organization

Introduction

Immunoglobulin E (IgE)-mediated allergic disorders are rising in prevalence in developed countries [1]. In the United States, one out of 4-5 individuals are estimated to suffer from IgE-mediated allergic diseases, and the improvement of environmental hygiene has been implicated in the increase of allergic diseases [2]. Given the high frequency of allergic diseases present in the general population, individuals with intellectual disability and limited expressive language (LEL) are expected to have allergic diseases at similar high frequencies.

In this manuscript, LEL is defined as an ability to use expressive spoken language being markedly below the age-appropriate level. Thus, given our reliance of detailed clinical history, evaluation of allergic conditions is much more difficult in LEL subjects. Consequently, LEL subjects are often under-diagnosed and under-treated for common allergic conditions in our experience.

An additional challenge is the behavioral symptoms that LEL subjects often exhibit. It should be noted that allergic conditions can exacerbate neuropsychiatric conditions. Epidemiological studies overwhelmingly indicate triggering and/or aggravating effects of allergic diseases on neuropsychiatric conditions in the general population. These include anxiety disorder, obsessive-compulsive disorders (OCD), and attention deficit hyperactivity disorders (ADHD). Unfortunately, many LEL subjects already suffer from various neuropsychiatric symptoms, depending on their underlying neuropsychiatric conditions. Therefore, in LEL subjects with baseline behavioral symptoms, there may be aggravation of neuropsychiatric symptoms due to pain and discomfort associated with allergic diseases. However, the impact of allergic conditions on behavioral symptoms may be easily missed by the caregivers and caring physicians due to the patients' limited communication skills. This may lead to under-treatment of allergic conditions and excessive use of neuropsychiatric medications, which are ineffective in such occasions. This will also frustrate LEL subjects, further exacerbating behavioral symptoms.

This review paper was prepared based on the author's experience that proper treatment of allergic diseases in LEL patients is important for improving their quality of life (QOL). In this review, discussion will be limited to the medical conditions mediated by the IgE- and non-IgE-mediated immune mechanisms. However, in the latter part of this review, we will also discuss the potential effects of other conditions often included in "allergy" by non- allergy/immunology (A/I) practitioners.

Neuropsychiatric symptoms associated with IgE- and non-IgE-mediated immune disorders

Allergic diseases may differ in definition depending on the caregivers' medical background and medical providers' specialties. Non-medical care-givers and medical care-givers who are not trained in the discipline of A/I may apply the word "allergy" to disease conditions not associated with IgE-mediated immune responses. In contrast, subspecialists with A/I training separate IgE-mediated immediate reactions from non-IgE-mediated reactions that may or may not involve immune mechanisms. Asthma, a common childhood respiratory disease, is triggered by multiple environmental factors and

not solely attributed to IgE-mediated immune responses. Thus, asthma is often subdivided into atopic asthma and non-atopic asthma in the A/I field. However, physicians not trained in the A/I discipline may regard asthma as a single allergic condition. This makes it difficult to assess epidemiological data based on survey results/billing codes. Keeping this in mind, I will summarize previous epidemiological studies addressing a relationship between allergic disorders and neuropsychiatric conditions first.

Allergic disorders and neuropsychiatric conditions: In most epidemiological studies, asthma and other allergic diseases are defined on the basis of clinical diagnosis, and whether or not the individual has IgE-mediated reactivity to allergens is not well documented. Population studies also tend to combine asthma, allergic rhinitis (AR), eczema, and food allergy into one group, not dissociating IgE mediated vs. non-IgE mediated conditions. Despite such limitations, epidemiological studies consistently support a positive association between allergic diseases and neuropsychiatric symptoms as reviewed several years ago [3]. The results of more recent population studies [4-6] are summarized in Table 1.

1	<p>Allergic disorders¹</p> <ul style="list-style-type: none"> Increased risk of at least on co-morbid psychiatric or behavioral disorder (ADHD, depression, anxiety, conduct/oppositional disorder and learning delay) in children [5] Positive association of anxiety in adolescents [4] 59% increased risk of depression in adult patients [6]
2	<p>Asthma</p> <ul style="list-style-type: none"> Increased risk of ADHD in children with asthma [7] Positive association with internalizing disorders (panic disorder, social phobia, separation anxiety, and total anxiety) with asthma as compared to non-asthmatic control children [8] Increase in frequency of depression in girls with non-atopic asthma (Age 11-14 yrs) [9]² Three fold higher likelihood of emotional symptoms in children with non-atopic asthma as compared to non-asthmatic, age-matched controls [10]² More severe persistent asthma at 5 years of age was associated with increased odds of affective, anxiety, somatic, opposition/defiant, and conduct problems later (Ages 5-17 yr) [11]² Positive association between uncontrolled asthma and neuropsychiatric symptoms in children enrolled in a comprehensive asthma management program [12]² <p>A high prevalence of clinically significant depressive and anxiety symptoms in prednisone-dependent asthma than those with prednisone-independent asthma [13]²</p>
3	<p>Risk factors for asthma</p> <ul style="list-style-type: none"> Panic disorders and anxiety sensitivity are prospectively associated with poorer control of asthma in adults [14]² Anxiety is an independent risk factor for asthma and vice versa in a nationwide population study¹ [15] Presence of anxiety and depression assessed by questionnaires was associated with uncontrolled asthma and lower Asthma Control Test scores [16]²

¹Allergic disorders are generally based on survey results and/or billing codes. Allergic disorders include asthma, eczema, allergic rhinitis, and food allergy. Asthma was not separated into atopic vs. non-atopic asthma.

²Asthma is well characterized.

Table 1: An association between neuropsychiatric conditions and allergic disorders and asthma (Summary of recent publications).

Recent studies also addressed whether any specific associations between neuropsychiatric symptoms and each atopic disease exist. Such studies are most frequently done in asthma patients [7-13], as also summarized in Table 1. Overall, these results indicate the *importance of asthma control for neuropsychiatric symptoms* (Table 1). However, it should also be noted that some studies report the presence of psychiatric conditions as risk factors of asthma as well as inadequate control of asthma (Table 1) [14-16]. These results indicate that the co-presence of neuropsychiatric conditions and allergic diseases make disease control more difficult, even in individuals with normal expressive language.

Other studies also addressed an association between other common allergic conditions such as AR and neuropsychiatric conditions (Table 2) [17-24]. In addition, other chronic conditions that are often cared for in the A/I clinic such as chronic sinusitis, have been reported to be associated with neuropsychiatric symptoms (Table 2).

For example, many studies have reported a positive association between neuropsychiatric conditions and AD which may be partly due to persistent pruritus [25]. Results of some recent studies in AD [26-28] are also summarized in Table 2.

1	<p>Allergic Rhinitis (AR)</p> <ul style="list-style-type: none"> • A higher prevalence of ADHD in children with AR [17,20,22]¹ • Increased risk of depression and suicidal ideation, which was further aggravated by sleep deprivation caused by AR in adolescents [19]¹ • Positive association between AR in early adolescence and depression in late adolescence and early adulthood [18]¹ • Increased risk of being depressed in the presence of rhinitis [21]² • AR diagnosis at age 4 year was positively associated with higher internalizing³, anxiety, and depressive scores at 7 yr in children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study [23]² • Increase in ADHD symptoms in AR patients along with increased parental stress [22]² • AR is associated with a higher risk of depressive disorder, anxiety and ADHD in German population study [24]¹
2	<p>Atopic dermatitis (AD)</p> <ul style="list-style-type: none"> • A higher prevalence of mental disorders (ADHD, depression, anxiety, and conduct disorder) in children with AD [26]¹ • Consistent positive association between AD and ADHD in meta-analysis [27] • Positive association between itching intensity in AD and depression symptoms [25]⁴ • An increased risk of developing major depress, any depressive disorder, and anxiety disorders in later life in individuals suffering from AD in adolescence and adulthood in a population study [28]¹
3	<p>Chronic rhinosinusitis (CRS)</p> <ul style="list-style-type: none"> • Higher pre-morbid prevalence of anxiety, headaches, gastroesophageal reflux disease, and sleep apnea in CRS patients [29]¹ • Positive association between CRS diagnosis and higher scores of anxiety and depression questionnaires [30]⁴ • Olfactory loss in CRS was positively associated with anxiety and depression symptoms in adults [31]⁴ • High prevalence of anxiety in CRS patients and less improvement of QOL following endoscopic sinus surgery in the presence of anxiety [32]⁴
<p>¹AR/AD/CRS diagnosis was based on self-reported survey results and billing code</p> <p>²AR was verified by skin prick testing and physical examination by physician.</p> <p>³DSM-5 (Diagnostic and statistical manual of mental disorders, 5th edition) categorizes OCD, depressive disorders, anxiety disorders, and post-traumatic stress disorders as internalizing disorders.</p> <p>⁴AD and CRS was well characterized by physician.</p>	

Table 2: An association between neuropsychiatric conditions and allergic rhinitis, atopic dermatitis, and chronic sinusitis (Summary of recent publications).

AR is a major predisposing factor for chronic rhinosinusitis (CRS) and sinusitis is implicated with asthma pathogenesis [33]. Therefore, not surprisingly, CRS has also been reported to have positive association with neuropsychiatric symptoms in population studies (Table 2) [29-32]. In summary, most epidemiological study results indicate that chronic inflammation caused or aggravated by allergic diseases impact neuropsychiatric symptoms.

Possible mechanistic link between IgE- and non-IgE-mediated immune conditions and neuropsychiatric disorders

If neuropsychiatric symptoms are truly seen in patients with allergic diseases at higher prevalence than in non-allergic subjects, the question arises whether allergic conditions are more frequently seen in established neuropsychiatric conditions. If so, it may be questioned whether allergen-induced inflammation is associated with the onset and progress of common pediatric neuropsychiatric conditions, such as autism spectrum disorders (ASD), and ADHD.

Several studies addressing the possible high frequency of allergic diseases in patients with neuropsychiatric conditions as summarized previously, generally describing equivalent frequency of allergic diseases as in the general population [3]. However, patients diagnosed with ADHD and tic disorder are often reported to have a higher prevalence of AR and other allergic conditions (Table 3) [34-36].

More recent studies have addressed a possible causal relationship between allergic diseases and chronic inflammation and the development of certain neuropsychiatric conditions. Results of 2 such studies are as follows:

- In a study utilizing two Danish nation-wide population-based registries, hospital contact with any allergic disorders (AD, urticaria, and AR) was found to increase a risk of schizophrenia (RR 1.59) [37].
- In 14,812 subjects diagnosed with atopic diseases (asthma, AD, AR, or allergic conjunctivitis) before 3 years of age during 1997-2000 who were followed until 2010, authors reported an increased risk of diagnosis of ADHD and ASD as compared to 6,955 non-atopic controls [38].

In these population studies, diagnoses of asthma, AR, and eczema are mainly based on the parental report or diagnostic codes used for billing. Therefore, asthma, eczema, and AR likely involve both atopic and non-atopic (non-IgE-mediated) conditions. It is difficult to assess the degree to which IgE-mediated allergic reactions are associated with the apparent high prevalence of asthma, rhinitis, and eczema in patients with the above-described neuropsychiatric conditions. Nevertheless, inflammation associated with asthma, eczema, and rhinitis may have aggravated the onset and progress of the above-described neuropsychiatric conditions, irrespective of IgE- or non-IgE-mediated immune mechanisms. In fact, three studies reported a possible link between inflammation caused either IgE-mediated or non-IgE-mediated mechanisms and exacerbation of neuropsychiatric conditions (Table 3) [39-41]. Interestingly, in the study of asthma/eczema patients, authors report that diagnoses of eczema and/or asthma were associated with increased serum levels of inflammatory markers [interleukin-6 (IL-6) and C-reactive protein (CRP)] [41]. These results may indicate a role for allergen-induced inflammation in the onset of psychotic conditions in genetically predisposed individuals.

1	<p>Prevalence of allergic disease in neuropsychiatric conditions</p> <ul style="list-style-type: none"> • A higher risk of asthma and AR in ADHD subjects in a population study [35]¹ • A higher prevalence of AR, asthma, AD, and allergic conjunctivitis in patients diagnosed with ADHD and/or tic disorders [34]¹ • A positive association between tic disorder/OCD and AR and eczema [36]²
2	<p>Possible link between immune mediated inflammation and exacerbation of neuropsychiatric conditions</p> <ul style="list-style-type: none"> • Worsening depression scores during allergy season in bipolar patients [39]² • A higher serum IgG antibodies against gut organisms and common food proteins in schizophrenia patients than normal controls, most evident in IgG antibody levels against <i>Saccharomyces cerevisiae</i> (ASCA) [40]. • Increased risk of psychotic experience at 13 years of age in children diagnosed with eczema, asthma or bot at 10 years of age [41]
3	<p>A role of neuro-immune network in a positive association between allergic diseases and neuropsychiatric conditions</p> <ul style="list-style-type: none"> • Increased risk of ADHD later in life with elevated inflammatory cytokine and other inflammatory mediators [42] • Changes in functions of the brain regions including anterior cingulate cortex and prefrontal cortex following peripheral immune activation [42] • Stress and anxiety affects ST reactivity in allergen induced inflammation [43-45] • Evidence of stress and subsequent neuro-immunological activation for allergy flare and adult-onset asthma [44,46]
<p>¹Diagnosis and asthma, AD, AR, and allergic conjunctivitis were based on survey results and/or billing code [34].</p> <p>²AR and other allergic conditions were physician diagnosed utilizing skin testing, and other laboratory measures along clinical features.</p>	

Table 3: Prevalence of allergic diseases in neuropsychiatric conditions and possible link between allergic inflammation and neuropsychiatric conditions.

Based on results of the above described studies, inflammation may be one of the links between neuropsychiatric symptoms and allergic diseases manifested by both IgE and non-IgE mediated mechanisms. It has been shown that inflammation triggered by psychological stress affects behavioral symptoms [47]. In research of depression and schizophrenia, two major neuropsychiatric conditions, the role of inflammatory cytokines involved in stress responses to the brain has been implicated with onset and progress of these conditions [47,48]. In these processes, inflammatory cytokines associated with innate immune responses are reported to play a major role.

Such neuro-immune interactions may also be true in other neuropsychiatric conditions with altered stress responses. Given the fact that allergic diseases cause chronic inflammation, it may not be surprising that impaired stress responses connecting the neuroimmune network has been proposed as one of mechanisms that cause neuropsychiatric symptoms in patients with allergic diseases. The results of some representative studies supporting this possibility [42-46,49] are also summarized in Table 3.

Neuropsychiatric components associated with allergic diseases are likely multi-factorial, involving genetic, social, and environmental factors. Despite the technical difficulty of addressing mechanisms between neuropsychiatric symptoms and allergic conditions, progress has been made, indicating the role of inflammation, for example as summarized in Figure 1 on the basis of study results shown in Table 3. In addition, mounting evidence indicate the effects of neuropsychiatric symptoms on QOL on patients suffering from allergic diseases. Awareness of neuropsychiatric aspect of allergic conditions may even more critical when treating subjects with LEL as described in the next section.

The association between allergic diseases and neuropsychiatric symptoms in LEL subjects

In our pediatric allergy/immunology clinic, many LEL children are those diagnosed with autism spectrum disorders (ASD). Although ASD subjects are markedly heterogeneous, immune mediated inflammation has long been suspected as one of major contributing factors to the onset and progress of the disease in some ASD subjects.

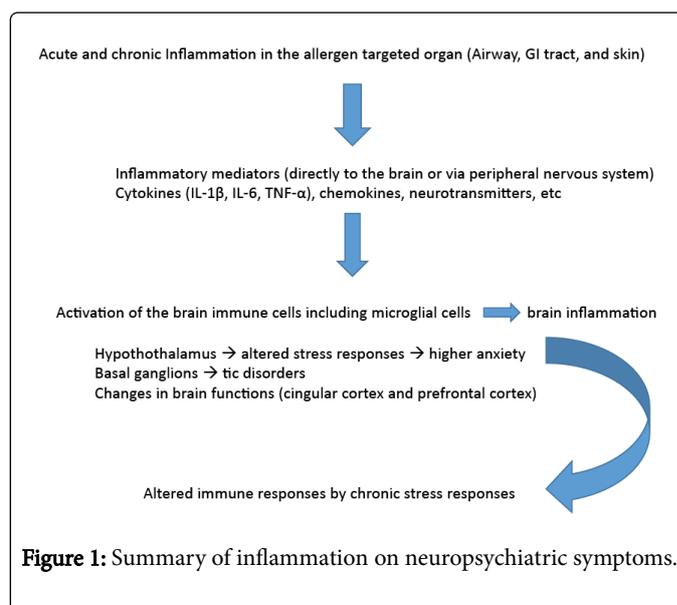


Figure 1: Summary of inflammation on neuropsychiatric symptoms.

The role of inflammation may be best studied in an animal model of ASD, so-called maternal immune activation (MIA). In rodent models of MIA, inflammation is typically induced during mid-gestation triggered by activation of innate immunity using endotoxin or other stimulants of innate immunity. Then changes in behavioral symptoms, inflammatory markers, and brain physiology/anatomy have been investigated in offspring. In the MIA model, offspring from mothers with MIA exhibit persistent behavioral changes even in adulthood. One of the proposed mechanisms in the MIA model is priming of microglial cells in the brain [50]. In fact, infection has been shown to be associated with schizophrenia and autism [50]. However, mechanisms of MIA induced brain damage may be multi-factorial [51].

Apart from infection, inflammation induced by allergic diseases may also have significant impact on LEL patients suffering from ASD and schizophrenia. In such cases, severity of allergic conditions may be

associated with onset and progress of neuropsychiatric conditions. One recent study indicated an association between ASD and allergic diseases in a dose-dependent manner as described below:

- Longitudinal cohort of children enrolled in Taiwan's National Health Insurance program between 2000-2010 (N=387,262) was used for assessing a risk of developing ASD and ADHD in patients with atopic dermatitis diagnosed before 2 years of age. Their results indicated an increased hazard ratio (HR) for ASD by 10%, with higher HR with disease severity and development of respiratory allergy diseases [52].

As mentioned previously, increase serum levels of inflammatory markers (IL-6 and CRP) were reported in children with asthma and eczema and this was positively associated with psychotic experiences later in adolescence [41]. This study may indicate the importance of inflammation caused by uncontrolled allergic diseases. Controlling allergic conditions in early life may be especially important for ASD children, given the results of the MIA models.

Clinical approaches in caring for LEL patients with allergic diseases

Given the above-described results, it is reasonable to assume that neuropsychiatric symptoms associated with both IgE- and non-IgE-mediated "allergic diseases" affects LEL patients at least at equivalent levels, as seen in the general population. In LEL subjects, behavioral symptoms are already present, partly associated with LEL that is caused by their primary neuropsychiatric disorders. Exacerbation of neuropsychiatric conditions caused by allergic diseases may be even more aggravated by frustrations and fears caused by the lack of appreciation of their allergy-related medical conditions by their caregivers. However, studies addressing effects of allergic diseases on QOL of LEL subjects have been scant. Nevertheless, studies focused on subjects with intellectual and developmental disabilities (IDD) have been repeatedly showing health disparities, associated with multiple factors, that include lack of access to appropriate medical care and also inappropriate training/preparation by medical caregivers that meet specific health need for IDD subjects [53].

Triggers or aggravating factors of behavioral symptoms in LEL subjects may not be simply attributed to the pain and discomfort associated with allergic diseases, but may also be associated with frustration and despair from not being able to explain his/her pain and discomfort. In addition, certain neuropsychiatric conditions that LEL subjects often suffer from may be associated with inflammation as discussed in the previous section. In such conditions, additional inflammation caused by allergic diseases may further exacerbate the components of his/her primary diseases. Therefore, controlling inflammation caused by allergic disease is important in improving QOL in LEL subjects by providing the best health outcomes. Having said so, there is limited data supporting this assumption.

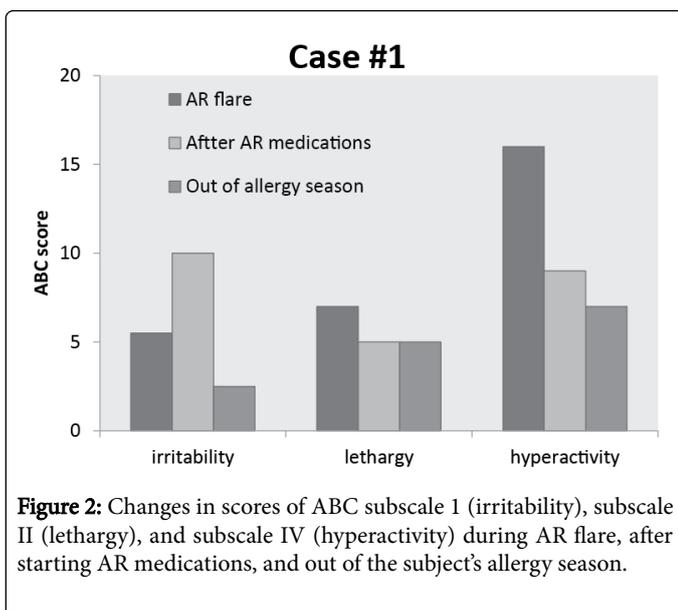
In the author's pediatric A/I clinic, most LEL subjects are those suffering from developmental disorders including ASD, and cerebral palsy (CP). In pediatric LEL/IDD subjects, behavioral symptoms are likely to change with brain development and onset of allergy diseases will further modify behavioral symptoms, creating confusing clinical pictures. This emphasizes an important role of primary care physicians (PCPs) in monitoring general health conditions of LEL/IDD subjects closely. However, this may be a daunting task for PCPs.

For example, difficulty in caring for ASD children in primary care settings has been well recognized. Secondary to their limited communications skills and problematic behavioral symptoms often present in ASD children, adopting the current 'medical home' model' to ASD children has been more difficult in ASD children than in children without ASD [53,54]. In addition, medical professionals who take care of ASD children may be skewed to developmental pediatricians, neurologists, psychiatrists, and neuropsychologists. They may lack training in taking care of allergic diseases. These facts are reflected in the recent research as summarized below:

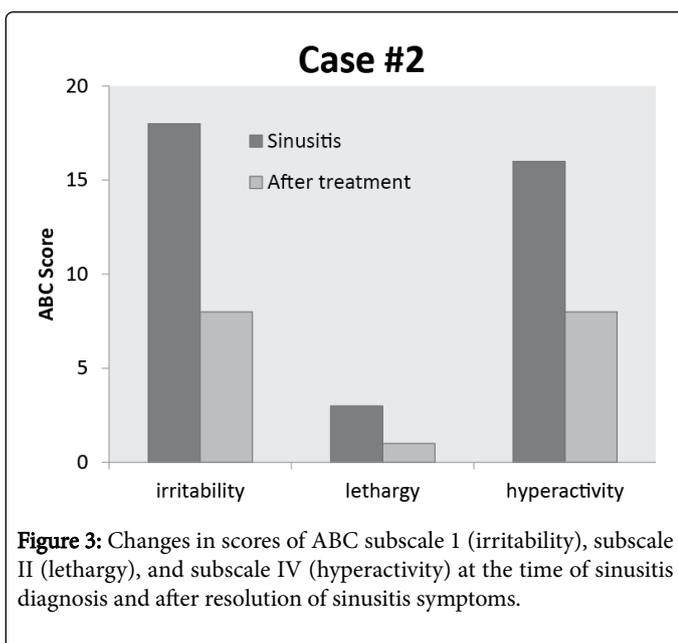
- Primary care consistent with that in a medical home care model was less likely to be provided to ASD children (odd ratio (OR) 0.45), as compared to children with asthma (OR 1.17) and those with other special health care needs on the basis of National Survey for Children's Health 2003-2004 [54].
- Mortality is reported to be higher in adults diagnosed with ASD than non-ASD subjects in a longitudinal cohort study of children born in Denmark from 1980 to 2010 (N=1,912,904).
- There is a high incidence of co-morbid conditions including allergy in ASD adults (N=255, Age 18-71 years) in cross-sectional study [55], based on survey results.
- A 2009-2010 survey of children with special health care needs (CSHCN) revealed that health care quality indicators in ASD subjects (N=3,025) was met to recommended levels at much lower rate (7.4%) than in those with functional limitations or those without ASD/functional limitation (10.5% (N=6,505), and 21.0% (N=28,296), respectively) [56].

Previously, we reported 2 cases of LEL children who revealed marked improvement of neuropsychiatric symptoms following xolair treatment for allergic rhinitis [57]. However, we have experienced many other cases that benefited with the 1st line treatment for common medical conditions. In the following section, we will present such representative ASD cases, that experienced significant clinical improvement in behavioral symptoms following standard treatment for common A/I conditions, as evidenced in improvement of scores of (Aberrant Behavior Checklist: ABC).

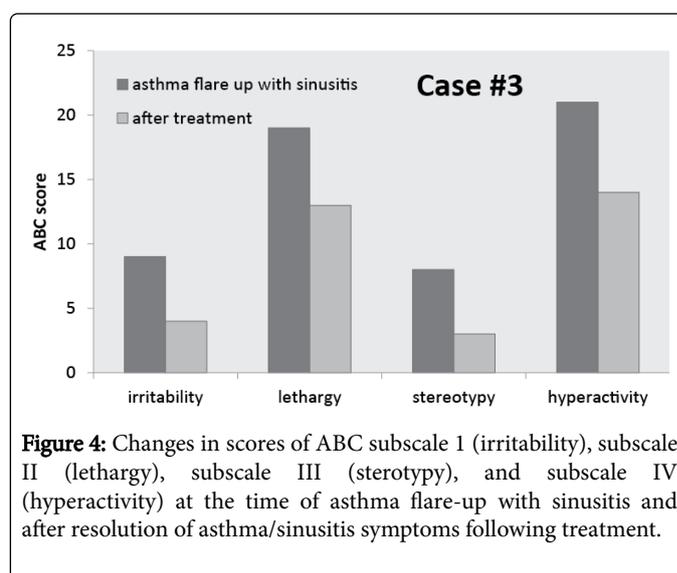
Case 1 – A high functioning ASD child with fluctuating behavioral symptoms following AR flare ups: A 9 year-old Caucasian boy with high-functioning ASD was presented with his mother, who was concerned over marked exacerbation of hyperactivity, OCD behaviors, and uncontrollable behaviors in the classroom during spring allergy season. These symptoms were not controlled with neuropsychiatric medications or behavioral interventions. He was diagnosed with AR elsewhere prior, with positive PST reactivity, but has been treated only with over-the-counter (OTC) allergy medications. The 1st line allergy medications (steroid nasal inhalers, montelukast, and ketotifen ophthalmic solutions) were started, without anti-histamines, secondary to parental report of his worsening agitation even with non-sedative anti-histamines. This resulted in marked improvement in ABC symptoms scores (ABC) (Figure 2). In his case, worsening AR symptoms might be associated with high pollen counts and increase in allergen exposure in his school environment.



Case 2 – A case of sinusitis: A 12 year-old non-verbal Caucasian boy with previously diagnosed with autism and aeroallergen allergy (tree and grass pollens) and food allergy (peanut) was presented, with his mother. His mother was concerned with worsening irritability and hyperactivity, in addition to onset of self-injurious behaviors (banging head and pinching himself). He remained afebrile and his mother reported absence of coughing or nasal secretion. However, sinus headache was suspected from his pattern of self-injurious behaviors, and presence of thick discolored nasal secretion in the nares. Under clinical diagnosis of sinusitis, he was treated with antibiotics (azithromycin due to previous history of penicillin induced urticaria) and a mucolytic (guaifenesin). His self-injurious behaviors resolved within 4-5 days in addition to improvement of his other behavioral symptoms (Figure 3). In his case, absence of nasal secretion at initial presentation was likely due to excessive use of OTC diphenhydramine.



Case 3 – A case of asthma and sinusitis: A 12 year old Caucasian girl diagnosed with non-verbal autism was presented with her mother who was concerned about her daughter's worsening behavioral symptoms (anxiety, OCD, and hyperactivity). She also started pinching her mother, which is frequently seen when she is getting sick. She was diagnosed with acute sinusitis complicated with asthma exacerbation on the basis of her physical findings of thick mucoid, discolored nasal secretion, and decreased air entry to her lung, although her mother did not notice wheezing, chronic coughing, or discolored nasal secretion; she was incapable to have spirometry. She was treated with montelukast, a steroid nasal inhaler (mometasone), antibiotics, and nebulizer treatment with budesonide and albuterol; she was unable to take meter dose inhalers. Her behavioral symptoms improved within 2-3 weeks. Interestingly, stereotypy symptoms are not typically affected with flare-up of allergy conditions in our experience, but in her case, we observed improvement in stereotypy scores (Figure 4). Her asthma is considered to be non-atopic asthma, with previously negative skin test reactivity and negative allergen specific serum IgE.



Conclusion remarks

The representative cases described above, illustrate challenges that may be encountered in subjects with IDD, especially those with LEL. Even easily treatable allergic conditions may be overlooked in PCPs' clinics and may be presented in the A/I clinic. However, many parents may never bring their children to the A/I clinic, because visiting to the clinic of subspecialists may be difficult with problematic behavioral symptoms. Careful evaluation of each individual and the development of individualized treatment measures is crucial for these patients. At a high frequency, these patients are also treated by unconventional treatment measures promoted by medical professionals practicing alternate and complementary medicine. These measures are generally not covered by insurance and a financial burden to the family. This makes it even more important to promptly and properly diagnose and treat common allergy conditions in individuals with IDD/LEL.

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