EXPERT REVIEWS

Autism spectrum disorders and allergy: observation from a pediatric allergy/immunology clinic

Expert Rev. Clin. Immunol. 6(3), 397–411 (2010)

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IgE-mediated allergic diseases (e.g., allergic rhinoconjunctivitis, atopic asthma and food allergy) are prevalent (up to 30%) in the general population and are increasing in developed countries. In infants and young children, non-IgE-mediated food allergy is also prevalent. In addition to easily recognized organ-specific symptoms, allergic diseases can cause neuropsychiatric symptoms, such as irritability and hyperactivity, in otherwise healthy individuals. This is also likely to occur in children with autism spectrum disorder (ASD). Moreover, the discomfort and pain associated with allergic diseases could aggravate behavioral symptoms in ASD children. Allergic conditions are easily treatable; however, ASD children may be underdiagnosed and/or undertreated for allergic and other common childhood diseases, in part due to their impaired communication skills. Practicing physicians should be aware of the potential impact of allergic diseases on behavioral symptoms and cognitive activity in ASD children. However, they also need to be aware that certain symptoms often attributed to 'allergy' by caregivers may not be immune mediated and should understand that behavioral symptoms can also be affected by many non-IgE-mediated causes.

Keywords: allergy • asthma • autism spectrum disorders • IgE-mediated allergic reactions • non-IgE-mediated 'allergic' reactions

Autism spectrum disorder (ASD) is a complex developmental disorder characterized by impaired speech, social interactions and repetitive aberrant behaviors. The etiology of ASD is not well understood except for a small percentage of children (≤10–15%) with known genetic mutations [1]. In the remainder of ASD children, ASD diagnosis is based on subjective behavioral symptoms, although recent studies have begun to elucidate the effects of genetic variations on ASD phenotypes [1,2]. Behavioral symptoms in ASD children change as the child develops and can be affected by multiple factors, including underlying medical conditions. Therefore, current diagnostic criteria of ASD inevitably result in encompassing markedly heterogeneous patient populations.

Autism spectrum disorder children are known to suffer from multiple comorbidities, with gastrointestinal (GI) and sleep disorders being the most common [3,4]. Certain behavioral symptoms are implicated with GI discomfort or pain [3]. Parents of ASD children who experience GI symptoms often report an improvement in certain behaviors along with resolution of GI symptoms following implementation of dietary intervention measures, such as a casein-free/gluten-free diet. Such observations indicate that food allergy (FA) may impact the behavioral symptoms observed in some ASD children.

Allergic reactions can be divided into two categories: immediate and delayed-type reactions. Immediate allergic reactions are mediated by IgE antibody (Ab) bound to the high-affinity IgE receptor (FcεRI) expressed on effector cells (mast cells and basophils) [5]. Thus, binding of allergen to cell surface IgE Ab rapidly activates effector cells, causing the release of inflammatory mediators within minutes upon allergen exposure [5,6]. This results in an acute onset of 'allergic' symptoms. Allergic diseases (e.g., allergic rhinitis [AR], allergic conjunctivitis, IgE-mediated FA and atopic asthma) are common in developed countries. The prevalence of atopy (allergic diseases) is 25–30% in the general population and is rising [7,8], along with the prevalence of non-atopic asthma [9]. Non-IgE-mediated food allergy,

 10.1586/ECI.10.18 ISSN 1744-666X

in which allergic symptoms manifest hours after exposure to the offending food, is also common in young children. Delayed onset of symptoms in non-IgE-mediated food allergy makes it challenging to diagnose in all children, irrespective of ASD status [10].

Retrospective analysis of ASD children evaluated in our pediatric allergy/immunology clinic indicates that allergic diseases are prevalent in ASD children, with a frequency equivalent to that in the general population [10,11]. Unfortunately, owing to their impaired expressive language, aberrant behaviors and lower tolerance to diagnostic measures compared with typically developing children, diagnosing allergic diseases may be more challenging in ASD children[12]. It has been our experience that ASD children are generally underdiagnosed and undertreated for allergic diseases as well as other nonallergic diseases that are common in children.

In our experience, parents of ASD children often present with concerns that their child may have an 'allergy' owing to the clinical features observed in their child. Very frequently, such 'allergy' symptoms are not associated with IgE-mediated or non-IgE-mediated immune reactions. It is very easy for practicing physicians to be overwhelmed when dealing with such ASD children and parents. Moreover, it needs to be emphasized that the behavioral changes observed in ASD children can be the result of many causes, and differentiating the effects of comorbidities on behavioral symptoms is rather challenging, as shown in attention deficit/hyperactivity disorder (ADHD) children [13,14]. We stress that allergic disorders are only one of the things to consider if underlying medical conditions are suspected. Moreover, even if allergic disorders are associated with behavioral changes, the effects of allergic diseases can be quite variable in each individual due to the influence of various environmental and genetic factors [15–18].

In this review, mechanisms of IgE- and non-IgE-mediated allergic/immune reactions will be summarized first, since these conditions are often confused by practicing general pediatrians and parents. Second, owing to the limited amount of literature involving the ASD population, the effects of both 'allergic' and 'nonallergic' common childhood diseases on behavioral symptoms will be discussed in both typically growing and ASD children. Lastly, the author will discuss 'what is allergy' and 'what is not allergy', a frequent concern expressed by parents of ASD children in our clinic.

This article will hopefully alert readers to the crucial role that practicing physicians play in caring for ASD children, as well as the importance of timely diagnosis and treatment of underlying allergic/nonallergic conditions that are easily treatable. This is important not only for the improvement of the general wellbeing of ASD children, but also because it may help to attenuate their behavioral symptoms by relieving pain and discomfort caused by underlying medical conditions. In turn, this may ultimately facilitate their cognitive development.

Mechanisms of IgE-mediated allergy & non-IgE-mediated immune reactions

The word 'allergy' is generally used to describe immediate immune reactions mediated by IgE Ab. The interactions between allergens and IgE Ab cause the rapid release of mediators from effector cells (i.e., mast cells and basophils), resulting in acute skin, airway and GI symptoms [5]. As opposed to IgE-mediated immune responses, non-IgE-mediated allergic reactions are mediated by non-IgE antibodies and/or cellular immune responses [19]. Delayed-type FA, for example, is thought to be mediated by allergen-specific cellular immune responses, with TNF-α being one of the main inflammatory mediators [19].

Table 1 summarizes IgE-mediated 'allergic' conditions as well as non-IgE-mediated conditions frequently seen in ASD children referred to the pediatric allergy/immunology clinic at our institution. The author will briefly summarize these conditions, including their pathogenesis, in this section.

IgE-mediated allergic reaction

Allergen sensitization & IgE synthesis

Most allergens are proteins that are taken up by antigen (Ag)-presenting cells (APCs), and then presented to T-helper (Th) cells as immunogenic peptides (epitopes) within the Ag-binding groove of MHC class II molecules [5]. Allergen presentation to Th cells leads to the differentiation of naive Th cells into Th2 effector cells in genetically predisposed (atopic) individuals [5,20]. Currently, it is not well understood how allergens preferentially induce Th2-cell differentiation in atopic individuals.

Th2 cells are characterized by the presence of a lineage-specific transcription factor (GATA3) and the production of Th2 cytokines (IL-4, IL-5, IL-13 and IL-25) [21]. Of these cytokines, IL-4 and IL-13 are critical for the synthesis of IgE, the key immunoglobulin (Ig) in immediate allergic reactions. Binding of IL-4 and IL-13 to their respective receptors leads to the activation of the transcription factor termed signal transduction and activation of transcription (STAT)6 [5,22,23]. This results in the transcription of Cε IgE genes. Additional signals for IgE synthesis are provided by ligation between CD40 ligand (CD40L) and CD40 expressed on Th cells and B cells, respectively [24]. That is, CD40L/CD40 interactions lead to the activation and translocation of NF-κB to the nucleus, initiating the transcription of two key enzymes (activation-induced cytidine deaminase and uracil nucleotide glycosylase), both of which are essential for Ig class switch recombination [24,25]. Following these events, B cells start producing IgE Ab.

Differentiation of Th2 cells and the actions of Th2 cytokines are counter-regulated by other Th-cell subsets, namely Th1 cells and Tregs [5]. For example, IFN-γ, a characteristic Th1 cytokine, and IL-10, a counter-regulatory cytokine produced by multiple lineage cells, including Tregs, both suppress differentiation of Th2 cells [5,21,26]. They also suppress the actions of Th2 cytokines [5,21,26]. Environmental exposure to Th1-inducing stimulants (e.g., endotoxin or livestock) during the first few years of life has decreased in developed countries with improvement of general hygiene. This change has been implicated in a general trend of increased prevalence of Th2-skewed allergic diseases in developed countries; this is commonly referred to as the 'hygiene hypothesis' [8,27]. Improvements in hygiene have also resulted in a lack of immunoregulatory stimuli from exposure to helminths [23]. This has also been shown to contribute to the increased prevalence of atopy in developed countries [23].

Previously, subtle changes of immunological parameters have been reported in ASD children, including Th1- or Th2-deviated cytokine levels, as reviewed elsewhere [10,28,29]. Specifically, higher plasma levels of Th1-associated cytokines were reported [30,31], along with increased Th1 cytokine levels in the limited numbers of brain tissues from autistic individuals [32], while others reported Th2-skewed cytokine levels/expression [33,34]. Moreover, Th17-deviated responses and evidence of mast cell activation have also been reported in ASD children [35,36]. The heterogeneity of ASD children may be the reason behind these conflicting data and the group that initially reported Th1-skewed responses attribute this to the presence of a subset of 'autoimmune ASD' [37]. In our previous studies, significant Th1- or Th2-skewed responses in ASD children were not observed [38,39]. However, the prevalence of atopic disease is as common in ASD children as in the general population [10,11,38,40].

Table 1. IgE-mediated and non IgE-mediated conditions seen in autism spectrum disorder children evaluated in the allergy/immunology clinic.

Condition	Diagnosis
Respiratory	
IgE-mediated	Allergic conjunctivitis Allergic rhinitis Atopic asthma
Non-IgE mediated	Nonallergic rhinitis Non-atopic asthma Recurrent or chronic rhinosinusitis[†] Gastroesophageal reflux disease Recurrent otitis media Adenoid hypertrophy
Gastrointestinal	
IgE-mediated	IgE-mediated food allergy
Non-IgE-mediated	Non-IgE-mediated food allergy (food protein-induced enterocolitis syndrome) Celiac disease
Overlapping conditions[‡]	Eosinophilic esophagitis Eosinophilic gastritis Eosinophilic enterocolitis
Skin	
IgE-mediated	Extrinsic eczema (often associated with IgE-mediated food allergy)
Non-IgE-mediated	Intrinsic eczema

[†]Chronic rhinosinusitis can also be associated with antibody deficiency syndrome, including common variable immunodeficiency and specific polysaccharide deficiency.
[‡]Eosinophilic esophagitis and other eosinophilic syndromes may be more frequently evaluated in the pediatric gastroenterology clinic due to the requirement for endoscopic examination for diagnosis, and are not discussed in detail in this review.

IgE & effector cells

IgE Ab is distinct from other subsets of Ig: first, IgE is present in a minute amount, far less than most other isotypes of Ig (e.g., IgA, IgG and IgM), and turns over rapidly in the serum (serum half-life: 2–3 days); second, IgE stabilizes when bound to high-affinity IgE receptors (FcεRI) expressed on mast cells and basophils; and third, the affinity of IgE Ab for Ag (allergens) is much greater than any other class of Ig. Thus, exposure to even minute amounts of allergen results in a cross-linking of IgE Abs on the cell surface of effector cells [23]. This results in activation of the FcεRI-expressing effector cells (mast cells and basophils), causing the release of various mediators, including histamine, leukotrienes and interleukins within minutes of allergen exposure [41].

It is believed that Th2-mediated immune defense developed against large extracellular organisms, such as helminths, and that IgE is a key factor in such a mechanism. However, unlike allergic diseases, helminth infection also induces systemic immune suppression exerted by Tregs and other suppressive cells [23]. That is, typical defense to helminth infection is thought to evolve into downregulated systemic proinflammatory responses, activated tissue repair and tightly controlled antiparasite Th2 responses in the mucosal locus [23]. By contrast, allergen-induced Th2 responses lack such suppressive components, leading to uncontrolled inflammatory responses. In other words, allergic diseases may be regarded as the result of ill-adapted Th2 responses.

Atopic diseases are associated with allergen sensitization in genetically predisposed individuals. Although seldom fatal, allergic disorders impose significant morbidity in the general population secondary to the chronic nature of the disease. This is evidenced by the mounting medical cost and loss of productivity (missed work/school days) associated with allergic diseases [7]. Discomfort and pain associated with allergic diseases are also known to cause psychiatric and neurological conditions in 'normal' individuals and will be discussed later in this review. This is probably also true for ASD children and has been observed in our clinic. It has been our experience that in ASD children, behavioral changes caused by both IgE- and non-IgE-mediated diseases are often attributed to just being 'autistic' and no proper diagnosis and treatment for the child's condition was implemented prior to their arrival at our facility. Our observation indicates the need for physicians involved in the care of ASD children to be aware of the importance of diagnosing common allergic as well as nonallergic diseases in these children. It is also important for the physician to not attribute certain symptoms displayed by ASD children to just being 'autistic', even if the symptoms are frequently associated with ASD.

Non-IgE-mediated immune diseases (conditions) associated with respiratory & GI symptoms

Nonallergic rhinitis

Rhinitis is a common condition affecting up to 25% of the general population [42]. Rhinitis is subdivided into two categories, depending on the presence or absence of allergen-specific IgE Abs; AR and nonallergic rhinitis. The etiology of nonallergic rhinitis is not well understood and is thought to be heterogeneous. Various terms have been used to refer to nonallergic rhinitis, including: noninfectious, nonallergic rhinitis; nonallergic, noninfectious, perennial eosinophilic rhinitis; and nonallergic rhinitis with eosinophilic syndrome. The latter two are characterized by the presence of eosinophils in nasal mucosa [42]. Since the terminology is confusing, we will briefly discuss known or suspected causes of nonallergic rhinitis.

Young children, including ASD children we have treated, often demonstrate nasal congestion with exposure to cold air. This is called 'cold air-induced rhinitis' – in adults, unilateral challenge of cold air was seen to induce the release of mast-cell mediators bilaterally, indicating involvement of neural reflex [6,43]. The mechanisms of this condition are not well understood; however, evidence indicates the presence of neural hyperresponsiveness that is mediated by capsaicin-sensitive sensory nerves [44].

Rhinitis is also associated with the ingestion of certain drugs. Aspirin-induced rhinitis is well known in association with nonatopic asthma and nasal polyp [42,45] but this condition is seldom seen in children. Likewise, the prolonged use of topical decongestants can cause rebound nasal congestion (rhinitis medicamentosa), which is much less frequent in the pediatric population [42,45]. Rhinitis also occurs with changes in hormonal balance, such as during pregnancy and the menstrual cycle, at the onset of puberty or with hypothyroidism [42].

The remaining types of rhinitis are of unknown etiology and are generally categorized as idiopathic rhinitis. Although its etiology is probably heterogeneous, idiopathic rhinitis is generally characterized by hyperreactivity of the nasal mucosa. The proposed etiology of idiopathic rhinitis includes autonomic neural dysfunction and upregulated tachykinin responses [42,45]. Such conditions are thought to lead to 'neuroinflammation', resulting in inflammation of the local mucosa with subsequent activation of the mucosal immune system [42]. IgE-mediated immune responses localized to the nasal mucosa have been reported in a subset of patients with idiopathic rhinitis [42,45].

In children, anatomical causes of chronic rhinitis, such as adenoid hypertrophy, also need to be taken into consideration. This is a predisposing factor for recurrent ear/sinus infection and obstructive sleep apnea in infants and young children [46–48]. Since disturbed sleep is a well-known comorbidity in ASD children [4], hypertrophy of adenoids and tonsils should be ruled out as a possible contributing factor to sleep disturbance in young ASD children.

Nonatopic asthma

Nonatopic (intrinsic) asthma is defined as asthma in the absence of allergen-specific IgE antibodies and accounts for approximately 20% of the asthma population [49]. In adults, occupational asthma and drug-induced asthma account for a large number of cases of nonatopic asthma [49]. In infants and young children, wheezing commonly occurs following infection [50]. Respiratory tract infection in early infancy/childhood and persistent allergen sensitization during preschool years are independently associated with the risk of developing asthma [9]. Decreased lung function in infancy is also a risk factor for airway hyperresponsiveness [51]. A genetic risk factor for low lung functions and the immunogenotype skewed to Th2 responses are thought to be associated with the development of asthma [9]. It was proposed that nonatopic asthma patients may lack persistent aeroallergen sensitization [9].

The most common cause of acute exacerbations of asthma is a viral respiratory infection, with rhinovirus being the most common causative organism [50]. Evidence indicates that asthma patients with recurrent asthma exacerbations have suboptimal production of IFN-γ and type 1 interferons, which are crucial for eradicating viral pathogens [52]. The risk factors for recurrent exacerbation of asthma also include chronic rhinosinusitis (CRS), gastroesophageal reflux disease, history of pneumonia, and impaired immune functions (immunodeficiency) [53,54]. Hypersensitivity to non-steroidal anti-inflammatory drugs (mainly for adults), psychiatric conditions such as depression, morbid obesity and social factors (e.g., lack of medical insurance) also impose a risk of recurrent asthma exacerbation [53,54]. However, previous reports also indicate a negative association between ADHD and asthma [55].

In summary, patients with nonatopic asthma may share a similar genetic predisposition for developing asthma as individuals diagnosed with atopic asthma. The resultant airway inflammatory condition needs to be treated effectively in order to prevent recurrent exacerbations of asthma. However, it has been our experience that treating asthma in autistic children may be much more challenging than in typically developing children. For example, ASD children may not be physically or developmentally capable of using standard asthma medications such as metered-dosed inhalers. It has been our experience that some ASD children do not tolerate nebulizer treatments owing to sensory integration disorders (they are intolerant to the noise caused by a nebulizer or unable to tolerate the placement of a mask on their faces). In either case, early diagnosis and proper education of parents regarding asthma is extremely important in order to provide optimal asthma treatment for both 'normal' and ASD children. Early signs of asthma such as frequent coughing may be overlooked secondary to the lack of complaints of shortness of breath or chest tightness in ASD children owing to their limited expressive language. Parents and primary care physicians need to be aware that asthma-induced respiratory distress can potentially worsen behavioral symptoms in ASD children, as will be discussed in the next section.

Rhinosinusitis/otitis media

Sinusitis and otitis media (OM) often cause significant respiratory symptoms. Although OM may be easily diagnosed by otoscopic examination, diagnosis of OM in ASD children may be more challenging since, based on our experience, these children are generally more resistant to physical examination, including

ear examination [56]. Acute sinusitis is often diagnosed on the basis of clinical findings, since CT scan causes exposure to high doses of irradiation [57]. However, we have experienced difficulty in diagnosing sinusitis in children due to their impaired expressive language and the presence of aberrant behaviors. In some cases, we also find it challenging to obtain a clinical history and/or positive physical findings indicating sinusitis in ASD children.

Chronic rhinosinusitis is often suspected with persistent purulent rhinorrhea and sinus symptoms despite appropriate antibiosis [57]. Since not all CRS patients present with typical clinical features, CRS may also be more difficult to diagnose in the general population without a CT scan [57]. Chronic rhinitis, both atopic and nonatopic, is a leading predisposing factor for CRS [58]. However, other underlying conditions also predispose individuals to CRS. These include immunodeficiency (mainly Ab-deficiency syndromes), cystic fibrosis, anatomical (mechanical) problems such as adenoid/tonsillar hypertrophy and nasal polyposis (mainly in adults), and the presence of systemic diseases such as vasculitis [57]. Both sinusitis and asthma are implicated in mucosal susceptibility to environmental stimuli. In addition, sinusitis is one of the major triggers for asthma [59]. This is probably also the case for ASD children. In our pediatric allergy/immunology clinic, we observed a high frequency of nonatopic asthma in ASD children diagnosed with CRS [10].

Celiac disease

Celiac disease (CD) is now considered to be an immune-mediated enteropathy caused by wheat protein ingestion in susceptible individuals, most of whom carry HLA-DQ2 or DQ8 molecules [60,61]. Tissue transglutaminase (tTG) was identified as the dominant autoantigen in CD. Serological screening of CD depends on the presence of anti-tTG Ab [60] as well as Ab against synthetic deamidated gliadin peptides [62]. However, histology remains the 'gold standard' for CD diagnosis. tTG, a calcium-dependent enzyme, is thought to form new Ags with gliadin-derived peptides by deamidation of gliadin glutamines to glutamates [60]. Deamidated gliadin peptides bind tightly to HLA-DQ2/DQ8 heterodimers [63]. Anti-tTG antibodies are detected in most CD patients and react to multiple conformational epitopes of tTG, as well as the gliadin fraction of wheat protein [64]. In addition to GI inflammation, CD patients manifest a variety of non-GI symptoms (atypical CD) and may even be totally asymptomatic (silent CD) [60,65,66]. The prevalence of CD is now considered to be much higher than initially thought [60].

Given its relatively high prevalence and varied clinical manifestations, CD is often included in the differential diagnoses for ASD children with GI symptoms [67]. One case study reported autistic symptoms in a child with untreated CD and deficiency of multiple micronutrients [68]. Resolution of behavioral symptoms occurred following the implementation of a gluten-free diet and proper supplementation of nutrients [68]. However, others report a low prevalence of neurologic and psychiatric symptoms in CD children compared with adult CD patients [69]. It should be noted that a recent epidemiological study indicated a possible association between maternal CD and the development of autism [70].

Non-IgE-mediated food allergy

During the first few years of life, aberrant immune reactions to food proteins are likely to occur more frequently. This is due to the immature gut mucosal immune system [19]. Therefore, during the first few years of life, non-IgE-mediated FA (NFA) is probably more common than potentially life-threatening IgE-mediated FA. In contrast to IgE-mediated FA, NFA symptoms typically occur hours after exposure, rendering it difficult to appreciate a causal relationship between exposure to the offending food and resulting clinical symptoms. In addition, no diagnostic measures for NFA are readily available for primary care physicians to utilize. As a result, NFA is frequently underdiagnosed even in the general population, despite the fact that presence of NFA has been described in the literature for more than 60 years [19]. This leaves the parents of NFA patients very frustrated, since these NFA children remain undiagnosed despite persistent GI symptoms.

Non-IgE-mediated food allergy to cow's milk protein (CMP) was initially reported in the 1940s, describing infants with bloody diarrhea and resolution of symptoms following the implementation of a dairy-free diet [71]. Since then, infants with non-IgE-mediated immune reactivity to CMP and soy have been described as having a wide range of clinical features. This condition is currently often referred to as food protein-induced enterocolitis syndrome (FPIES) [72]. Determination of reactivity to the offending food (mainly milk and soy) is generally based on *in vivo* responses – that is, the resolution of GI symptoms with avoidance of the offending food and recurrence of symptoms following oral challenge. Most patients with NFA lack skin-prick test reactivity or food-allergen-specific IgE [72,73].

Food protein-induced enterocolitis syndrome often manifests as infantile colic and recurrent vomiting during early infancy. On the other hand, diarrhea and loose stool are more common clinical findings in older infants and young children [19]. In cases with severe FPIES, clinical features may resemble sepsis with lethargy, hypotension, dehydration, abdominal distention and acidemia [74]. These patients may also reveal hypoalbuminemia and failure to thrive (FTT) [72]. In patients with severe FPIES, reintroduction of the offending food can cause shock, despite the absence of IgE antibodies [74,75]. The immune mechanisms of FPIES are not well understood. However, evidence indicates a crucial role of aberrant cellular immune reactivity to food proteins with the production of proinflammatory cytokines such as TNF-α, along with impaired oral tolerance, in the development of NFA [19,74].

Although it can be potentially life-threatening in very severe cases, such instances are rare and the prognosis of FPIES is generally excellent. Resolution of symptoms is typically expected to occur within a few weeks following the implementation of an elimination diet (ED) [73]. It is also known that many infants with NFA to CMP and soy eventually outgrow this condition, establishing oral tolerance in the gut mucosal immune system [76]. This may also be the case in ASD children. In our clinic, we diagnose FPIES more frequently in younger ASD children (<6 years of age) than older children. In our previous studies assessing IgE- and non-IgE-mediated FA in ASD children, we found a fairly high frequency

of FPIES against milk protein in young ASD children (2–6 years of age) [10,40]. In typically growing children without ASD, FPIES resolves by 3–4 years of age. However, it is our observation that ASD children may take longer to outgrow FPIES. This may be partly attributed to difficulty of diagnosing FPIES in this population and subsequent under-diagnosis and delayed introduction of treatment measures [10].

Possible effects of allergic & nonallergic disorders on cognition & behavioral symptoms

Allergic and nonallergic diseases causing chronic airway and gut mucosal inflammation may induce or aggravate psychiatric conditions. This may be due to disease-associated stress, pain, discomfort and sleep deprivation that will be discussed in this section. Studies addressing such aspects of allergic and nonallergic diseases are scant. Nevertheless, the limited data available and our clinical findings indicate the importance of recognizing underlying allergic/nonallergic conditions in association with behavioral symptoms.

Neuropsychiatric effects of allergic & nonallergic diseases in the general population

Allergic rhinitis

Two studies examined young individuals with seasonal AR due to pollen allergy [77,78]. The results indicated impaired cognitive learning as well as impaired memory in allergic patients. Symptoms such as fatigue were also attributed to the use of antihistamines with sedative effects [78]. However, AR patients given placebo also experienced fatigue and impaired cognitive learning [78]. Another case–control study involving 1814 students (aged 15–17 years) evaluated school performance during the grass pollen season [79]. The results supported previous findings showing a significant risk of lower national examination test scores in the presence of symptomatic AR and/or with the use of sedative antihistamines [79]. Other studies involving smaller numbers of subjects also revealed similar results [80].

In addition to the negative effects of AR on cognitive activity, impaired sleep is a well-recognized complication [80]. It is not unusual for AR patients to complain of a lack of 'a good night's sleep'. A study that examined the quality of sleep in adult AR patients showed that there was a positive correlation between disturbed sleep and the severity of AR [81].

The effects of AR on behavioral symptoms, such as irritability, have been recognized by practitioners. One study reported a high prevalence of AR in patients with ADHD, indicating a role of AR in aggravating ADHD symptoms [82]. In this study, AR was validated by examining skin-prick test reactivity. Another study, analyzing healthcare claims databases indicated higher rates of depression and anxiety disorders in AR patients [83]. However, it should be noted that in this study, validation of AR diagnosis was not undertaken.

Asthma

Practicing physicians have long suspected that asthma has an effect on mental illnesses and/or behavioral symptoms. Epidemiological studies indicate an increased frequency of anxiety and panic symptoms/disorders in asthma patients [84]. In a study using a large community sample (n = 4181 including 236 asthma patients aged 18–65 years), patients with physician-diagnosed asthma and current (within 4 weeks) asthma symptoms revealed an increased likelihood of any anxiety disorders, specific phobia, panic disorder and panic attacks [85]. A high prevalence of panic attacks in asthma patients in both adults and children was also reported in multiple studies that utilized both clinical and community samples [84,86–89]. In studies focused on populations without documented psychological disorders, asthma was positively associated with later development of internalizing symptoms and panic disorders [90–92].

How does asthma affect the previously described mental disorders? The etiology of this association is probably very complex and varies with each individual. Proposed theories regarding the association between asthma and mental conditions include somatic effects of hyperventilation, hypersensitivity of CO_2 receptors in the brain, the effects of asthma medications, and mutual genetic/environmental factors predisposing for asthma and panic/anxiety disorders such as maladaptation to stress [84].

Autism spectrum disorder children who are referred to our pediatric allergy/immunology clinic often have many of the previously described behavioral symptoms. The presence of rhinitis and asthma probably aggravates behavioral symptoms in ASD children, as seen in patients with other psychiatric disorders. Therefore, from our experience [10], we believe that these common medical conditions should be kept in check when providing medical care for ASD children, although prospective studies addressing this assumption are necessary.

GI disorders

An association between IgE-mediated FA and the development of mental disorders is not well documented. However, it has been our observation that children with atopic dermatitis (AD) and FA are often irritable and exhibit a short attention span. Constant pruritus and GI irritation seem to be associated with such behaviors in the patients we have treated in our clinic (see cases 1 and 2 described later). In a population study, atopic eczema was associated with ADHD [13,93], although a negative association between childhood eczema and ADHD has also been reported [94,95].

In inflammatory bowel diseases, chronic GI inflammation, caused by autoimmune conditions, is often associated with behavioral symptoms as well as impaired cognitive activity. Interestingly, it was reported that in 35 ASD children with language regression, there was a positive association with both GI symptoms and family history of autoimmune diseases [96]. At this point, I will discuss neuropsychiatric symptoms observed in two GI conditions, CD and NFA, since they are frequently implicated with GI symptoms observed in ASD children.

Celiac disease

It is now known that the clinical manifestations of CD are highly variable and can manifest as neurological or psychiatric symptoms. Some neuropsychiatric manifestations may be explained by malnutrition or a deficiency in micronutrients that results from chronic GI inflammation. However, certain neuropsychiatric symptoms appear

to occur without notable nutrient deficiency. In studies involving 71 adult CD patients without detectable nutrient deficiency, 21 of these patients were shown to have neurological/psychiatric complications, including headache, depression, entrapment syndromes, peripheral neuropathy and epilepsy [97]. On the other hand, in a study evaluating a large number of CD children (n = 835), only 15 of them (1.79%) were noted to have neurologic/psychiatric problems, including epilepsy (n = 4), febrile seizures (n = 3), nonsyndromatic mental retardation (n = 2), chronic nonprogressive headache (n = 2) and bipolar disorders (n = 3) [69]. Based on these results, it appears that neuropsychiatric manifestations may be low in CD children. However, it is important to keep in mind that other autoimmune conditions that are frequently seen in CD children [98,99], as well as micronutrient deficiency, can cause neurological and psychiatric manifestations [98,99].

Non-IgE-mediated FA

As noted previously, severe NFA (food protein-induced enterocolitis syndrome) can lead to FTT and malnutrition [73]. Therefore, as with CD children, FTT and malnutrition may explain the worsening neuropsychiatric symptoms in NFA children. However, in our experience, NFA patients without notable nutrient deficiency often exhibit irritability, hyperactivity and a short attention span, similar to what is seen in children with atopic eczema. Such behavioral symptoms generally resolve or improve after implementation of a restricted diet that avoids the offending food [73]. In children treated in our clinic, parents of NFA children often comment that he/she is a 'different child' after implementation of the restricted diet.

Few published data exist regarding behavioral changes in non-ASD children with NFA. As part of one of our previous studies, behavioral changes in non-ASD children with NFA (n = 6; 2–4 years of age) were examined using an Aberrant Behavior Checklist (ABC) questionnaire [100] prior to and 3 months after implementation of the restricted diet. These non-ASD/NFA children were studied as NFA controls when studying behavioral changes in ASD/NFA children following dietary intervention [101]. Our results revealed a noticeable reduction in ABC subscales I (irritability) and IV (hyperactivity) in non-ASD/NFA children after implementation of the restricted diet (Figure 1). These results suggest that NFA-induced GI symptoms can impact behavioral symptoms (mainly irritability and hyperactivity) in children who do not have ASD. This may well also be the case in ASD children [101].

Effects of chronic medical conditions in ASD children

Individuals with developmental disabilities are likely to be at a greater risk of developing chronic and acute medical conditions than the general population, partly owing to poor communication skills. This has been demonstrated in several published studies, which will now be described.

A Swedish study examined subjects with developmental disabilities admitted to the hospital [102]. The results revealed that study subjects had at least one chronic medical condition and a threefold higher rate of hospital admissions than the general population [102]. Similar results were obtained in studies conducted in Australia and England. The Australian study revealed higher rates of medical consultations and hospital admissions in subjects with developmental disabilities (mental retardation) (aged 20–50 years; n = 202) than controls [103]. The English study showed that older individuals with developmental disabilities (aged >65 years; n = 134) had a higher frequency of medical conditions than controls [104].

It should be noted that these studies focused on individuals with mental retardation, not necessarily ASD. However, these results provide evidence that similar issues may also apply to individuals with ASD. As previously noted, in our experience, diagnoses of common childhood diseases are more difficult in ASD children than normally growing children. Therefore, when caring for an ASD child, it is imperative to keep common medical conditions in check, despite the difficulties associated with examining these children. The idea that allergic and nonallergic medical conditions, as described previously in this review, can affect behavioral symptoms in ASD children, is not really surprising, especially considering their effects on the general population. However, only a few studies have examined the effects of medical conditions on behavioral symptoms in ASD children and even fewer are of substantial quality in their research methodologies.

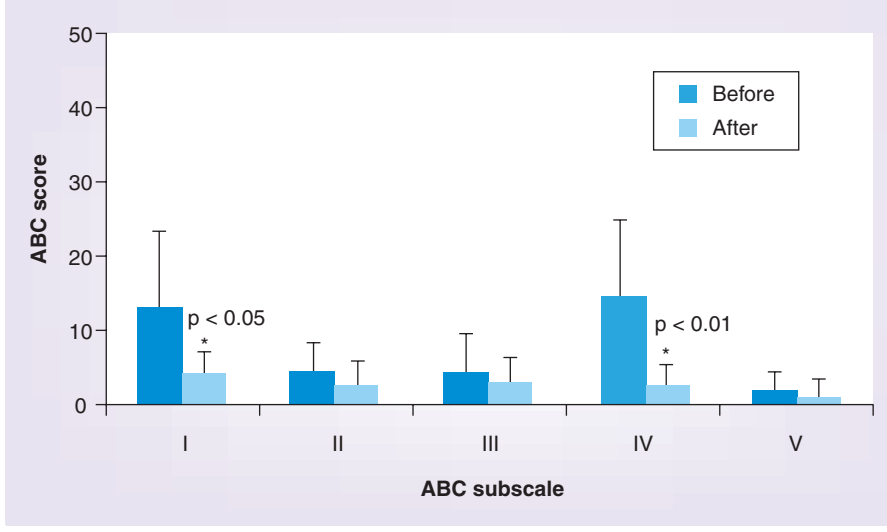


Figure 1. Changes in scores in each Aberrant Behavior Checklist subscale before and 3 months after dietary intervention in non-autism spectrum disorder children with non-IgE-mediated food allergy. ABC subscales: I (irritability), II (lethargy), III (stereotypy), IV (hyperactivity), V (inappropriate speech).
*Lower than values prior to dietary intervention (Wilcoxon signed ranks test).
Error bars denote standard deviations.
ABC: Aberrant Behavior Checklist.
Data obtained from USA Institutional Review Board-approved investigations in our clinic.

A number of studies have examined minimally verbal subjects, many of whom were autistic. It has been reported that in individuals with minimal verbal skills, problem behaviors such as aggression, self-injury and temper tantrums can vary with concurrent medical conditions [105,106]. Sleep deprivation and active allergic symptoms negatively affected problematic behaviors in individuals of 13, 15 and 18 years of age with mental retardation, aggression and self-injurious behaviors [107]. In Chiladiti's syndrome (interposition of the colon between the liver and the diaphragm), adult patients with mental retardation were found to exhibit GI symptoms (e.g., nausea, pain, vomiting, anorexia, abdominal distension and constipation) similar to those observed in the pediatric population, although this syndrome is generally asymptomatic in adults with normal cognitive activity [108]. In addition, an association between self-injurious behaviors and premenstrual syndrome was also reported in seven out of nine women with mental retardation [109].

As with normal individuals, proper medical intervention will probably lead to the improvement of behavioral symptoms caused by acute or chronic medical conditions in individuals with ASD and other mental disabilities. However, published data examining the effectiveness of medical intervention on problematic behaviors in individuals with developmental disabilities are extremely limited [106,110]. Carr *et al.* attempted to develop quantitative measures for assessing pain in minimally verbal individuals (n = 11; nine out of 11 diagnosed with autism) using questionnaires [106]. Results from the use of these questionnaires indicated significant behavioral changes with pain or discomfort in the study subjects [106]. In addition to changes in behavior, it may also be likely that underlying medical conditions affect cognitive activities in ASD children, as was observed in normal children with allergic disorders [79].

Using the pain scale developed by Carr *et al.*, as well as ABC questionnaires, we observed significant changes in the ABC scores of a few ASD children in our clinic when they experienced flare-ups of common childhood medical conditions (e.g., AR, asthma, NFA, CRS and recurrent ear infection). Three representative cases will now be described.

Case 1. An 8-year-old ASD child with severe IgE & non-IgE-mediated FA, AD & AR

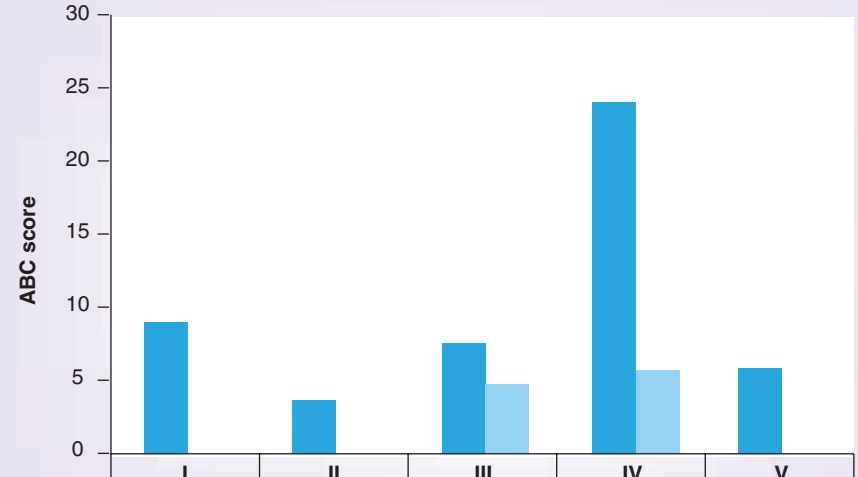
This child was diagnosed with pervasive developmental disorder – not otherwise specified and is high functional when his allergic conditions (food allergen-induced eczema, allergic rhinoconjunctivitis and non-IgE-mediated delayed-type FA) are under control. However, when experiencing a flare-up of seasonal allergy symptoms or when an accidental exposure to offending food occurs, his behavioral symptoms worsen markedly, affecting his school performance. Figure 2 illustrates how the ABC scores worsen when his medical conditions flare-up (i.e., when he was sick). In parallel to changes in the ABC score, his total pain scale became as high as 23 when he was sick as opposed to 0 when he is well.

Case 2. A 5-year-old ASD child with NFA

This child was diagnosed with autism with impaired expressive language but good receptive language. His behavioral symptoms, especially hyperactivity and irritability, were significantly worse with recurrence of NFA symptoms following accidental exposure to offending food. This is evidenced by changes of the ABC score (Figure 3).

Case 3. A 7-year-old child with nonverbal autism & untreated chronic sinusitis

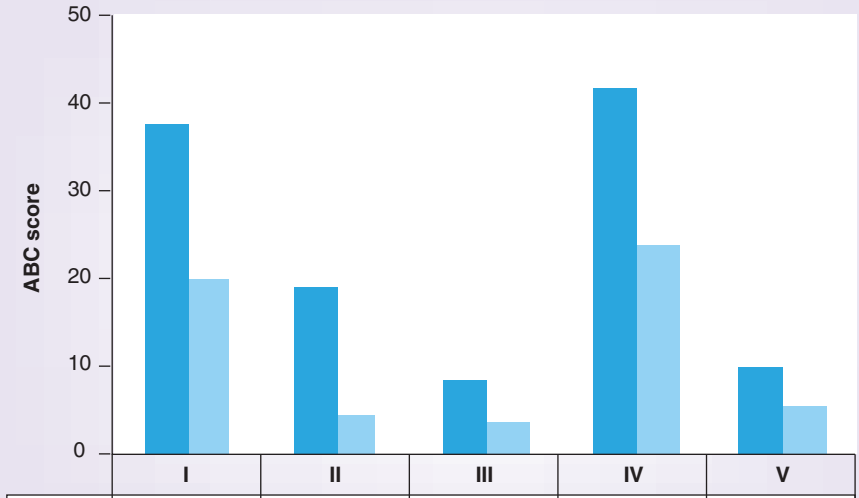
This nonverbal autistic child was diagnosed with recurrent OM and treated with frequent but short courses of antibiosis by his general pediatrician. His behaviors have been problematic, with extreme irritability and hyperactivity as well as self-injurious behaviors (e.g., biting hands, hitting and banging head). Placement of a pressure equalization tube did not relieve his ear symptoms. This child was revealed to have pansinusitis by sinus CT scan, despite being afebrile. He was treated with a prolonged course of intravenous and oral antibiotics, which rendered significant improvement in his behavioral symptoms, as evidenced by changes in the ABC score (Figure 4). His pain scale was high at 45 when he was sick and is at 11 now that he is well. In summary, changes in his ABC scores reflect behavioral changes affected by his illness.



	I	II	III	IV	V
Sick	9	4	8	24	6
Well	0	0	5	6	0

Figure 2. Changes in scores in each Aberrant Behavior Checklist subscale when this autism spectrum disorder child is sick or well in case 1. ABC subscales: I (irritability), II (lethargy), III (stereotypy), IV (hyperactivity), V (inappropriate speech). ABC: Aberrant Behavior Checklist.
Data obtained from USA Institutional Review Board-approved investigations in our clinic.

These three cases described in the previous paragraphs illustrate the potential effects of underlying common allergic and nonallergic medical conditions on behavioral symptoms in ASD children. In addition, such observations point out the importance of and need for practicing physicians to consider how sickness can affect individuals with ASD. However, it is important to note that, although our clinic treats a significant numbers of ASD children, our observations are based on a limited numbers of patients, and larger prospective studies are urgently needed to further address the effects of common medical conditions in these ASD children.

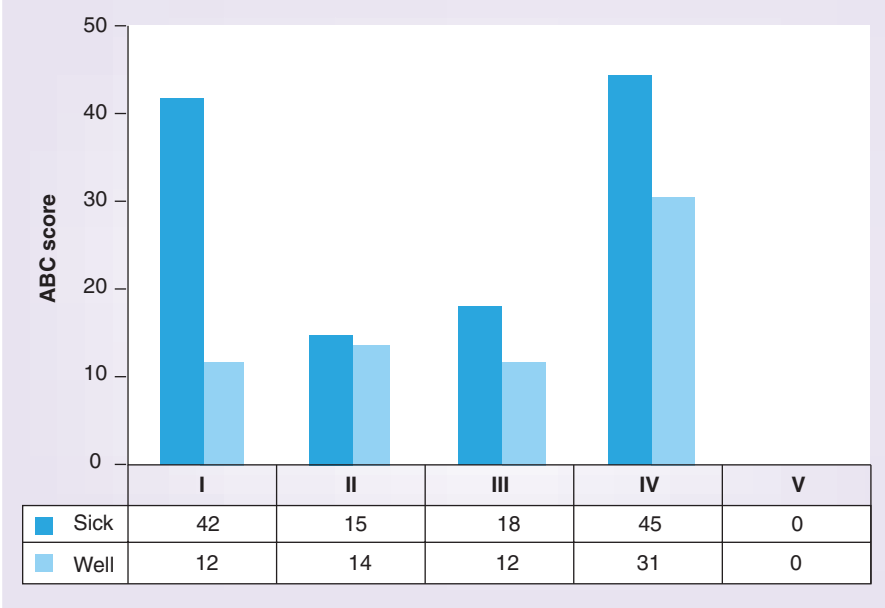


	I	II	III	IV	V
Sick	36	18	8	40	9
Well	19	4	4	23	5

Figure 3. Changes in scores in each Aberrant Behavior Checklist subscale when this autism spectrum disorder child is sick or well in case 2.
ABC subscales: I (irritability), II (lethargy), III (stereotypy), IV (hyperactivity), V (inappropriate speech).
ABC: Aberrant Behavior Checklist.
Data obtained from USA Institutional Review Board-approved investigations in our clinic.

Myth of 'allergy' – what is allergy & what is not allergy

The last part of this article will address the various clinical symptoms that parents attributed to 'allergy' in the ASD children evaluated in our pediatric allergy/immunology clinic. Practicing physicians need to be aware that many of the physical symptoms and clinical features that the parents of ASD children may attribute to 'allergy' are not necessarily associated with IgE-mediated allergic reactions or other immune responses. Typical symptoms described by parent to be 'allergy' in our experience are described below. This will hopefully help streamline treatment measures and avoid unnecessary diagnostic measures such as skin prick testing.



	I	II	III	IV	V
Sick	42	15	18	45	0
Well	12	14	12	31	0

Figure 4. Changes in scores in each Aberrant Behavior Checklist subscale when this autism spectrum disorder child is sick or well in case 3.
ABC subscales: I (irritability), II (lethargy), III (stereotypy), IV (hyperactivity), V (inappropriate speech).
ABC: Aberrant Behavior Checklist.
Data obtained from USA Institutional Review Board-approved investigations in our clinic.

Respiratory symptoms

Chronic nasal congestion

Chronic nasal congestion is frequently seen in young children [42]. It should be noted that aeroallergen sensitization develops gradually in atopic individuals, usually during the first several years of life [42,111,112]. Typically, atopic disorders manifest first as atopic eczema during infancy [111,112]. Chronic and/or seasonal aeroallergen exposure then evolves into clinical manifestations of atopic asthma and AR over the next few years of life – the so-called atopic march [112]. This is why positive skin test reactivity or aeroallergen-specific IgE are observed much less frequently in infants and young children [111]. As previously discussed, nonallergic (vasomotor) rhinitis is commonly seen in infants and young children, secondary to general hypersensitivity of nasal mucosa in this age group [42]. Thus, if the child lacks a positive family history of atopy and infantile eczema, chronic rhinitis is more likely to be associated with idiopathic 'vasomotor' rhinitis, which is

commonly seen in infants and young children. Careful history taking and thorough physical examination should be helpful in differentiating AR and nonallergic rhinitis in ASD children.

Headache

Headaches or sinus headaches may be attributed to 'allergy'. It is difficult to detect the presence of a headache in minimally verbal ASD children. However, behavioral symptoms, such as head banging and hitting/pressing on the ears, may be indicative of a headache. In our experience, this especially holds true if these symptoms vary from time to time. The possible causes of a suspected 'headache' should be carefully examined in these ASD children; these include nonallergic sinusitis, adenoid/tonsil hypertrophy, untreated rhinosinusitis (see case 3) and neurological causes, such as migraine and epilepsy, on the basis of the children treated in our clinic [10,11].

GI symptoms

Food allergy

Gastrointestinal symptoms commonly seen in the ASD children presented to our clinic include diarrhea, loose stool, GI cramping and constipation alternating with diarrhea and bloating. As previously mentioned, given these symptoms, both IgE and non-IgE-mediated FA may need to be considered as underlying medical conditions [10]. Both types of FA occur more frequently than other causes (e.g., metabolic disorders, genetic/infectious causes, neurological causes and autoimmune conditions) associated with chronic GI symptoms [10,113]. In addition, the treatment measures (restricted diet) are benign [10,113]. Therefore, possibilities of FA should be ruled out before considering the previously described less common causes associated with GI symptoms. The presence of a well-documented causal relationship between exposure to food allergens and onset of symptoms within 2 h indicates IgE-mediated FA [10]. In contrast to IgE-mediated FA, NFA, as previously discussed, may be more difficult to assess owing to the delayed onset of symptoms [10,19]. However, the presence of objective GI symptoms (e.g., constipation, loose stool and diarrhea) and a positive family history can help physicians consider if the patient should try a restricted diet [19,72]. In FPIES, the main causative food proteins are milk and soy [72]. Since many nondairy/nonsoy products are commercially available as substitutes, the trial of a dairy-free, soy-free diet may be easily implemented for a few weeks without causing nutritional deprivation if FPIES is suspected. In addition, prior to implementing a wheat-free diet, which is far more challenging to implement than a dairy- or soy-free diet, it may be helpful to run serological screenings for celiac disease [60], which were discussed previously.

Dysbiosis

It has been our experience that both ASD and non-ASD children with NFA often have candida enteritis. Etiology of this finding may be partly attributed to the deprivation of a source of probiotics (yogurt) in a dairy-free diet, since most NFA children react to cow's milk [72]. We have also noted that NFA children with chronic GI inflammation may experience invasive candida infections. In individuals with a genetic predisposition, candida enteritis can play a role in development of chronic gut inflammation, as indicated in patients with inflammatory bowel diseases [114–116]. Changes in commensal flora have also been associated with GI symptoms in ASD children [117,118]. Studies in rodent models of CNS inflammation showed behavioral effects of propionic acid, a metabolic end product of enteric bacteria, on behavioral symptoms when it was injected intraventricularly into the brain [119,120]. It should be noted that probiotics have been shown to attenuate GI inflammation in patients with inflammatory bowel diseases [19]. With this in mind, a trial of probiotics may be reasonable to consider in ASD children who are on a restricted diet or have skewed dietary habits. We have observed favorable effects from the use of probiotics in these clinical settings [Jyonouchi H *et al.* Unpublished Data].

Skin symptoms

Flushing

Parents of ASD children evaluated in our clinic are often concerned about flushing of their child's skin following ingestion of food or exposure to nonspecific irritants such as cold air. In general, such skin symptoms are not consistent with urticarial rash, lacking a pruritic migratory rash raised from the skin. In the cases we have examined, such flushing is generally short-lived and resolves within an hour or so with or without use of antihistamines and is very unlikely to be associated with IgE-mediated allergic reactions. Again, a detailed history will be helpful in differentiating such skin reactions, which may be associated with dysautonomic skin reactions, from IgE-mediated allergic skin reaction.

Eczema

Atopic dermatitis is roughly divided into two categories: intrinsic and extrinsic eczema [121]. Allergen sensitization and Th2-mediated IgE synthesis is thought to play a significant role in extrinsic eczema but not in intrinsic eczema [121]. Recent studies indicate that impaired formation of the skin epithelial barrier plays a crucial role of in the development of extrinsic and intrinsic eczema [121]. Filaggrin is thought to play a crucial role in the formation of the skin barrier [121,122]. Impaired skin barrier formation due to mutations in filaggrin genes has been implicated in subsequent sensitization to allergens, colonization of microbes and subsequent development of severe AD [121,122]. It should be noted that food allergen sensitization is not necessarily observed in all patients with AD. Thus, the elimination diet will only be effective in patients with documented reactivity to food allergens [123].

Adverse reactions to medications & other biological substances

Medications

Most of the adverse reactions to medications reported by parents in our clinic are not IgE-mediated. For example, more than 90% of immune reactivity to the first-generation penicillin is IgG-mediated [124]. If penicillin reactivity is mediated by IgE, the patient usually has previous exposure and experiences a rapid onset of symptoms upon their second exposure to penicillin [124]. Lack of such a history makes it very unlikely that the subject has an IgE-mediated penicillin allergy. IgE-mediated allergic reactions are much more

commonly seen with medications administered intravenously [124]. Delayed-type non-IgE-mediated reactions can occur with medications given by multiple routes (orally or non-orally) [125,126]. Importantly, skin prick testing is not appropriate for assessing such delayed-type reactivity [124]. Skin patch testing may be available for testing cellular reactivity to certain medications/chemicals [125]. Careful history taking is generally very useful in differentiating IgE from non-IgE-mediated reactions to medications.

Nonimmunogenic food components

For the most part, Th2-mediated IgE responses are generated against protein antigens [10]. Certain chemicals, such as penicillin, can bind to the carrier proteins and form neoantigens, thereby inducing conformational changes; the typical carrier protein is serum albumin [125]. These small chemicals are called 'haptens'. Large complex carbohydrates/lipids can cause immune responses; however, these are not directed by Th cells and, thus, seldom lead to IgE synthesis [127]. Parents of many ASD children evaluated in our clinic have presented with 'allergy' to non-protein chemicals lacking hapten activity or nonspecific irritants. An example of this is allergy to 'sunlight' that may really indicate sensitive skin or dysautonomic conditions. Practicing physicians need to educate parents about which symptoms can be 'allergic' and which are not.

Expert commentary

It is our clinic's experience that ASD children tend to be underdiagnosed and undertreated for common chronic medical conditions such as allergic disorders. This may be partly attributed to the difficulty in diagnosis due to their limited expressive language and behavioral symptoms such as aggression. We have found that treatment of common childhood illnesses, including allergic diseases, significantly improved behavioral symptoms and subsequent cognitive development. This may not be surprising considering the effects of allergic diseases and other disorders on neuropsychiatric symptoms/conditions documented in the general population. Practicing physicians should make themselves well aware of the possible effects of pain and discomfort caused by chronic illness on behavioral symptoms in ASD children. This will probably facilitate timely diagnosis and proper treatment of underlying medical conditions. On the other hand, all too frequently, many symptoms and clinical features not associated with IgE-mediated immune responses are attributed to 'allergy', prompting unnecessary allergy workups that may cause stress or anxiety in these ASD children. Proper evaluation of allergic versus nonallergic conditions in ASD children is important for optimal development. It is extremely important for both the parents and treating physician to be aware of these issues to avoid both unnecessary workups, and/or underdiagnosis or treatment.

Five-year view

Recently, the idea that the presence of various comorbidities in ASD children can exert effects on behavioral symptoms and cognitive development has become more accepted among physicians and therapists [3]. This is a trend that will probably increase over the next few years. With this, we hope to see more prospective studies that assess the effects of underlying medical conditions on behavioral symptoms and cognitive development in the ASD population. The author hopes that the results of such studies will help raise awareness and lead to a greater understanding of the relationship between medical conditions and behavioral changes by practicing physicians. In addition, the development of screening measures that can be used by practising physicians for assessing behavior changes associated with pain and discomfort will greatly benefit ASD children who suffer from common childhood illnesses. Although this may not be accomplished within the next 5 years, it is our hope that it will become a well-accepted concept/practice in 10 years time.

Financial & competing interests disclosure

This study was partly supported by funding from the Autism Research Institute (San Diego, CA, USA) and the Jonty Foundation (St Paul, MN, USA). The author is thankful to Lisa Huguenin for critically reviewing this manuscript. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Allergic disorders are equally prevalent in autism spectrum disorder (ASD) children and the general population. Our results revealed that ASD children also suffer from various chronic medical conditions at a high frequency.
- It has been our experience that chronic medical conditions, including allergic diseases, are often underdiagnosed and undertreated in ASD children. This is partly due to their impaired expressive language and other behavioral symptoms.
- In the general population, chronic inflammatory conditions affecting gastrointestinal and airway mucosa can cause significant neuropsychiatric symptoms/conditions, as reviewed in this study.
- The presence of chronic inflammatory conditions affecting gastrointestinal and airway mucosa can cause pain and discomfort, which in turn may significantly influence behavioral symptoms in ASD children.
- Patterns of behavioral symptoms can be used to help determine pain and discomfort in ASD children with limited expressive language.
- In order to facilitate diagnosis and treatment of underlying medical conditions, it will be extremely helpful for practicing physicians to become aware of the potential effects of underlying medical conditions on behavioral symptoms in ASD patients.
- In our experience, proper treatment of underlying medical conditions can significantly improve behavioral symptoms in ASD children.
- Many clinical conditions that are not caused by Th2-mediated IgE responses may often be attributed to an 'allergy' by the parents of ASD children, as observed in our clinic. Therefore, parents often seek an allergy workup for the child.

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