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Research Article

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A Novel Link between Early Life Allergen Exposure and Neuroimmune Development in Children

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Abstract

As COVID-19 unprecedented situation significantly increased the time families spend indoors, the awareness of unhealthy living conditions negatively impacting immune system and early neurodevelopment of children is of crucial importance. We retrospectively reviewed unrelated cases of the children with confirmed multiple indoor allergen sensitization due to prolonged exposure to unhealthy indoor environment with infestation and water damage, who, in addition to multiple health problems related to allergy and asthma, also developed neuroimmune complications and growth delay. Documented early in life atypical neurologic and behavioral changes were common in all cases. Clinical analysis did not establish other causative reason aside from prenatal and early life exposure to unhealthy living conditions. Alternaria Alternara and Penicillium/Aspergillus molds were found in all homes and sensitization was confirmed in all cases. Significant similarities in the symptoms recorded in all three families led us to a hypothesis that, likely, a significant level of the immune response to external immunogenic pathological stimulus such as mold spore protein, mycotoxin protein, dust mite protein, decay-related volatile particles (VOC) skewed a balance of the neuroimmune interactions, and further affected neuronal network establishment. As all children exhibited significant spectrum of the systemic inflammatory conditions early in life, coupled with inability to follow normal neurodevelopment, we hypothesize that an overwhelming activation of the aggressive immune mechanisms by the epigenetic factors led to glia activation, cytokine storm and break of tolerance. We hypothesize that developing immune system exhibited aggressive responses due to environmental danger signals; subsequently TH-1 or TH-2 switch enables multiple clinical syndromes development with atypical presentation due to the described novel mechanism. An increased due to the COVID-19 lock-down may increase an amount of exposure of vulnerable people to indoor biological particles and volatile organic compounds present in unhealthy buildings. It is of crucial importance to identify and remediate indoor exposure factors that can decrease immune protection, especially against infectious pathogens such as novel coronavirus.

Keywords: Mold, Water Damaged Building, Early Brain Development, Skin Test, Allergy to Mold, Toxic Exposure, Seizure, Atypical Seizure, Neurodevelopment, Aspergillus, Alternaria, Prenatal Mold Exposure, Behavioral Problem, Sublingual Allergy Drops, Immunotherapy.

Introduction

Currently a research field describing immune system role in the development of nervous system has been rapidly growing and accumulating evidence. Clinical multicenter trials confirmed early childhood neurological and autoimmune diseases overleap, thus prompting new considerations in diagnosis and management of children who have been exposed to various environmental factors. Children being born into or living in unhealthy living conditions with high levels of protein-based material capable of sensitization have become an important focus of research in preventive and environmental medicine. A special attention is drawn toward sensitizing airborne biological particles capable of overriding mechanisms of tolerance and driving allergic or autoimmune phenotype switch to TH-2 or TH-1 phenotype.

Due to pandemic of COVID-19 virus, many countries implemented a lock-down policy to prevent the spread of infection. At the same time, this measure significantly increases an exposure to indoor biological particles and volatile organic compounds present in unhealthy buildings. Such exposure is associated with increased incidence of many allergic and auto inflammatory diseases, and is one of the preventable causes of the immune imbalance such as asthma. It is of crucial importance to identify and remediate indoor exposure factors that can decrease immune protection against all infectious pathogens such as novel coronavirus.

Experimental Details

A retrospective analysis of 3 cases was performed. An exposure and clinical symptoms were analyzed and correlated. Skin prick test result for common indoor allergen testing was used to determine allergic sensitization to mold. The validity of the test was confirmed with Positive control (histamine) and Negative control (Glycerin). Results were read in 20 min and recorded 30 min following test administration. A positive test result was considered any reaction => 3mm induration per standard practice guidelines.

Case1

A two-year-old boy with the diagnosis of allergic rhinitis (AR), asthma, growth delay. Baby was born healthy at 38 weeks gestation that was carried in the house with "unhealthy conditions". Patient was brought into and subsequently exposed to the indoor environment for 2 years, were water intrusion, significant mold growth, construction decay, and mice infestation were discovered by an environmental company. Health problems reported by paediatrician: unexplained failure to thrive, frequent upper respiratory illness (every 4-6 weeks); wheezing and chronic nasal congestion. At three months of age, he was admitted and investigated for "atypical" continuous seizures with apnea. Epileptic seizure repeated 2 month later. Over 2 years of life, he had numerous hospitalizations for asthma, pneumonia, and bronchitis. Patient received nebulized bronchodilator treatments, antibiotics, oral steroids, epilepsy treatment and physiotherapy. Sensitization to indoor allergens was confirmed by an allergy skin test: multiple indoor molds, dust mite species, and cat antigen. No laboratory studies were available for review.

Intervention: All symptoms significantly improved following relocation and allergen avoidance measures. There were no other neurological problems since family moved to a mold-free housing, and seizure medication was successfully discontinued. Patient continued antihistamines and asthma controller. Positive trend in weight gain but persistent short stature (below 5th percentile).

Case 2

20-month-old baby boy presented with the diagnoses of AR, asthma, eczema, abnormal movements and crying spells of unknown etiology, growth retardation, and stridor. Pregnancy was carried in contaminated residence and the baby was born in above-mentioned residence. Baby was born with normal weight and height and had a documented good sucking reflux and good breastfeeding at discharge. He dropped over 2 percentile lines by the age of one month.

Problems with inconsolable crying attacks with unusual hand movements and feeding difficulties led to hospital visits. Over a year patient developed episodes of struggled periodic breathing with atypical head movements and leg movements, difficulty swallowing liquids. Patient was given a presumptive diagnosis of chronic croup, which did not respond to any treatments including courses of oral steroids and NSAIDS. After a hospitalization for one of these abnormal episodes, an investigation was initiated: chest xRay and rhinoscopy, bronchospy, pulmonary consultation, allergy consultation, sleep study and speech therapy. While no anatomical or infectious cause was identified, abnormal vocal cord closure with stridor was confirmed by laryngoscopy; chest xRay confirmed peribronchial thickening and hyperinflation; a sleep study revealed abnormal leg movements and periods of desaturations with apnea. Rashes first appeared almost after birth and gradually developed into blisters by the age of 4 months. Multiple diagnoses (seborrhea, hand/foot/mouth disease, dermatitis) were considered as none of the treatments provided improvements.

Laboratory analysis demonstrated multiple immunologic abnormalities (CH50>60, CD3 2313/ul, CD4 1665/ul, CD19 560/ul, white cell count 4.5k/ul, low neutrophil count at 16% and elevated lymphocytes 71%). Allergy testing at 18 month demonstrated clear positive reactions to molds (Aspergillus and Alternaria A.), at 20 month of age additional testing revealed positive reactions to molds and indoor allergens. An asthma diagnosis was made, and steroid inhaler treatment initiated with no success.

A household inspection revealed continuous unhealthy living conditions (water damage, mold growth, rodent and cockroach infestation).

Intervention: a paediatrician recommended immediate relocation followed by almost complete resolution of the atypical episodes and good weight gain. A significant growth problem remained with below fifth percentile height. Allergic rhinitis and asthma were controlled with medications, while desensitization was planned to start when the child gains full control of the swallowing.

After environmental report outlined unhealthy living conditions with high levels of molds, rodent and cockroach infestation, family vacated the property. Cough, stridor and congestions are continuous issues. He is currently on higher then recommended for his age steroid inhaler, bronchodilator, iron supplement, steroidal creams for eczema and antihistamine.

Case 3

A six years seven month old boy presented with AR, allergic otitis media, generalized idiopathic epilepsy, developmental delay, speech impairment and learning disability. He also was investigated for attention deficit disorder and aggressive behaviour.

He was born normal and was developing well until two years of age when a family moved in a residence with continuous water damage and significant mold growth (unbeknown by residents). During a period of 3 years, a child had progressive deterioration of development, cognitive skills, exhibited periods of uncontrolled aggression. He had multiple hospitalizations and workup for atypical seizure episodes. He was diagnosed with atypical benign Rolandic seizure disorder until he had a prolonged seizure unresponsive to treatment associated with a fall of the ceiling decayed by mold growth. During a three year period was tried on multiple medications with little success. Once a water leak and significant mold decay were discovered, the family relocated which associated with significant improvement of the symptoms and overall behavior. A seizure and aggression episode once again repeated later when another mold source was discovered in children's room.

Multiple blood tests confirmed many abnormal immunological markers (high CH50, high C4a complement, elevated TSH with normal T4) without a specific pattern; electroencephalogram demonstrated left and sporadic centrotemporal abnormal spikes atypical for known childhood seizures. Skin allergy test confirmed sensitization to multiple molds and outdoor allergens. Child was started on sublingual immunotherapy with gradual improvement of language, learning and behavioral skills. Within first six month of allergy treatment, he was able to regain lost social and self-care skills and was able to attend a regular school. There were no seizure activity; a seizure medication was successfully discontinued.

Following unsuccessful therapy for atypical seizures and behavioral problems (learning disability, aggression and attention deficit trends), one of the patients was placed on sublingual immunotherapy targeting identified allergen. An excellent improvement was observed with a significant improvement of the quality of life. No atypical seizures were recorded during a two-year observation time. A child was able to return to learning environment. Aggression and tantrums were controlled with the steady development of appropriate childhood

reactions. We observed two worsening episodes both connected to significant indoor mold exposures. Patient recovered after discovered exposure conditions were eliminated.

Results

Overall, the youngest two patients who were exposed during pregnancy and were brought into unhealthy conditions following delivery had most development problems: low birth weight, neonatal weight instability and growth delay, allergic rhino sinusitis, frequent hospitalizations and respiratory issues (Table 2). When looking at the combination of the clinical symptoms, one can identify similarities in all three children. It was clear to us that not only all symptoms, including neurological and developmental, coexisted in the situation of multiple indoor allergen sensitization, but also the same symptoms improved with allergen avoidance and allergen immunotherapy.

Table 1: Comparative characteristics of the clinical presentation relative to age of allergen exposure

Ade during exposure	Growth delay	Allergic rhinitis	Asthma	Allergic dermatitis	Motor problems	Behavioral problems	Speech delay
Prenatal to 2 y.o.	Present	Present	Present	Present	Present	Absent	Present
2 to 5 y.o.	Absent	Present	Absent	Absent	Present	Present	Present

In one child we find that early problems with inconsolable cry, repetitive jerky hand movements and inability to swallow may reflect abnormal brain wiring and pathological development of functions control. In addition, a second child showed loss of developmental milestones and motor functions.

We present a limited data on laboratory studies, which identifies various abnormalities of the blood analysis, but all together pointing to inflammatory reactions with engagement of complement. Due to retrospective data collection and very early age of the children, we could not further assess specific antibody formation, or changes in complement following interventions.

While multi-sensitization to indoor allergens was confirmed (Table 2) in all cases we found only certain mold species to be repeatedly found in highest counts in their homes by environmental groups, and confirmed in patients with skin test, which are Alternaria A., mixed Penicillium species, Aspergillus Fumigatus, Rhisopus and Fusarium species.

Table 2. Skin testing results.

Test (allergen) name	Case 1	Case 2	Case 3
Dog	Negative	Positive	n/a
Cat Pelt	Positive	Positive	n/a
Mite (D.P)	Negative	Negative	n/a
Mite (D.F)	Positive	Negative	n/a
Mixed Cockroach	Negative	Positive	n/a
Mouse	Negative	Positive	n/a
Alternaria	Positive	Positive	Positive
Claridosporum	Positive	Negative	Positive
Fusarium spp.	Positive	Positive	Positive
Drechslera	Positive	Positive	Negative
Penicillium, Mixed	Positive	Positive	Positive
Aspergillus niger	Negative	Positive	Negative
Aspergillus fumigatus	Positive	Positive	Positive
Epicoccum nigrum	Negative	Negative	Negative
Curvularia spp.	Positive	Negative	Negative
Aureobasidium	Positive	Positive	Negative
Rhizopus spp.	Positive	Positive	Positive
Stemphylces	Negative	Positive	Positive
Candida	Positive	Negative	Positive
Neurospora spp.	Positive	Negative	Positive
Mucor	Positive	Negative	Positive

Chaetomium	Negative	Positive	Negative
Yeast (Sacchor.)	Negative	Negative	Positive
Tricophython	Negative	Positive	Positive

Skin prick test result for common indoor allergen testing. The validity of the test was confirmed with Positive control (histamine) and Negative control (Glycerin). Results were read in 20 min and recorded 30 min following test administration. A positive test result was considered any reaction => 3mm induration per standard guidelines. Allergens which produced a positive reaction in all 3 cased are in bold. Case 3 is limited on the number of allergens tested due to significant concern of seizure activity.

Limited number of allergens tested due to significant concern of seizure activity in a child.

While we understand that we report only sporadic cases, a further investigation of these species in a relation to neurological problems in early childhood may exist and should be evaluated further. Environmental reports from the housholds of all three families identified multiple mold species that correlated to the sensitization panels in children with average 85% matching (more species were found in the environment as compared to positive skin prick tests).

Discussion

We postulate that abnormal immune response in children exposed to water damaged buildings with detectable mold growth and decay, which directly involves sensitization to allergen and overwhelming activation of inflammatory pathways, may be directly affecting early brain development and neuronal network activation, evoking biochemical instability of the neuronal functioning. As a result of prolonged cytokine release of activation of the allergic response, a seizure activity and behavioral instability of the child may be observed. As the immunotherapy, treatment alleviated neuroimmune problems and allowed a child to return to the normal level of functioning, we propose that allergen immunotherapy together with environmental allergen avoidance measures may be used as a treatment of the neurological and developmental problems in affected children.

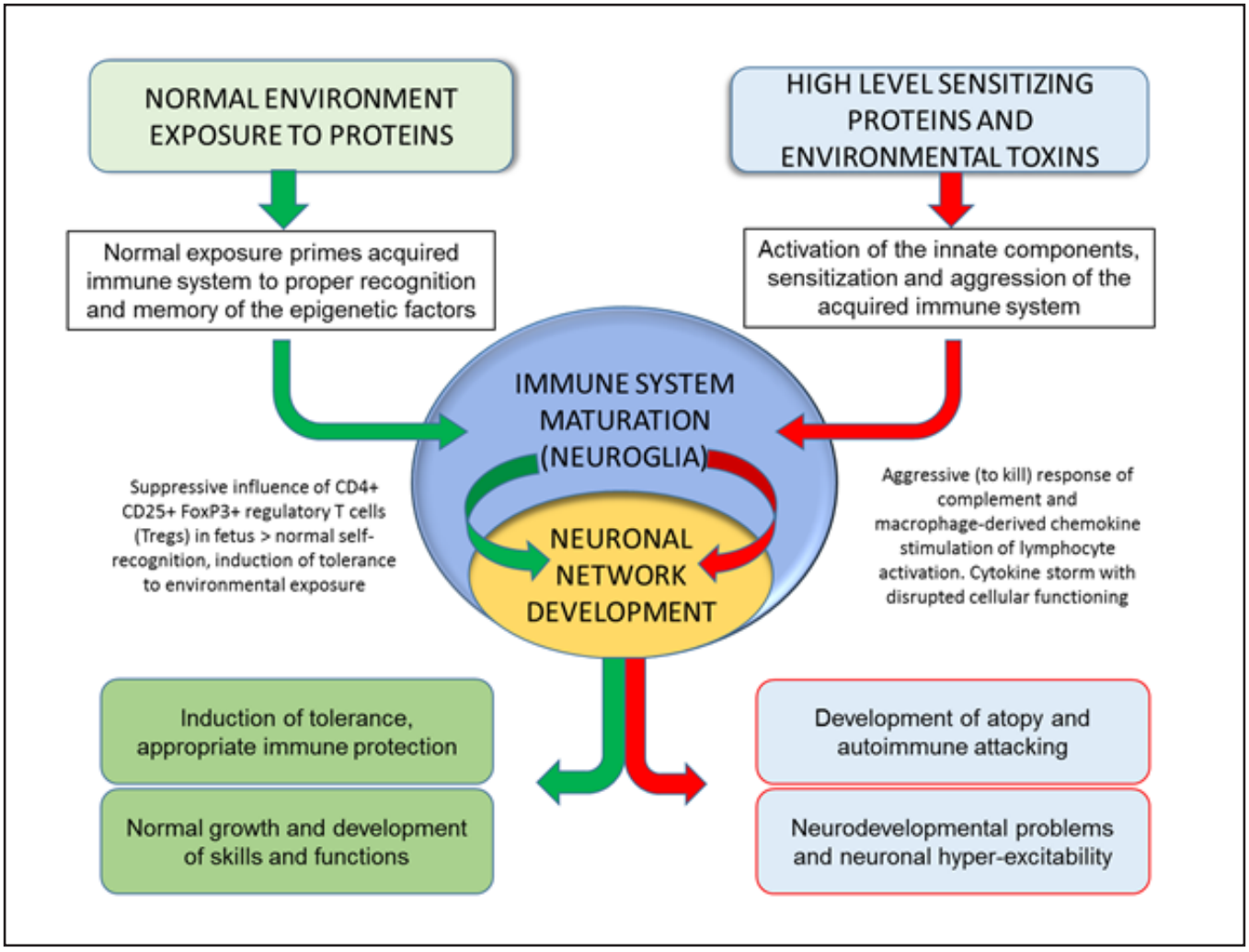
A number of environmental factors have been reported to affect the development and severity of asthma, including outdoor air pollutants (e.g., particulates, ozone), indoor irritants, and agents such as environmental tobacco smoke. However, it can be argued that the most significant inhaled agents that modulate the development of respiratory allergy and asthma are biologics [1]. Particulate matter PM10 exposure during pregnancy was reported as an association with the risk of a new diagnosis of asthma in recent studies, which becomes an additional risk factor predicting development of various inflammatory conditions future in life [2]. Allergic health concerns caused by dampness, exposure to particulate matter and indoor allergens include but not limited to allergic sinusitis, allergic otitis, allergic conjunctivitis and allergic (extrinsic) asthma [3, 4].

A significant concern over development of atopy due to exposure to allergens very early in life was previously studied in younger children. An exposure of a child with immature immune and nervous system leads to development of atopic conditions and sensitization to multiple allergens at four years of age [5]. Starting from the Developmental Origins of Health and Disease (DOHaD) hypotheses proposed by David Barker, namely fetal programming, in the past years, there is a growing evidence of the major role played by epigenetic factors during the early development period. The interactions between mother's exposures and responses, placenta and fetus immune system formation are now a focus for ongoing research. A specific immune responses of infants at birth to individual trigger factors associated with an underlying immaturity of cytokine production, is implicated in the development of subsequent allergic disease [6-8].

The relation between the immune system and epilepsy has been documented. Immune activation may precede or follow the appearance of seizures. Authors state that depending on the situation, the innate and acquired immunity may be involved to various degrees [9]. Epilepsy with documented seizures developing after infiltration of cells of the adaptive immune system in the central nervous system (CNS) include a broad range of disorders with different (known or unknown) etiologies [10]. Microglia, which provides neuronal support in the nervous system and have been implicated in complex neurodevelopmental programs such as neurogenesis and synaptic pruning, is also known to respond to cytokine, and metabolic signals derived from the local neural environment, and drive the refinement of functional neuronal circuits. Due to their constant surveillance of the brain parenchyma, involvement in development, and confirmed reactivity to both peripheral immune and microbiome-derived signals, microglia is a key cellular intermediate linking neurodevelopmental disorders such as autism and schizophrenia with microbiota influences in models of maternal immune activation (MIA) [11]. Autistic children exhibit evidence of oxidative stress and impaired methylation, which may reflect effects of toxic exposure on brain tissue metabolism. Recently oxidative stress and methylation, with particular emphasis on adaptive responses were studied. Methionine synthase activity is required for signaling process mediated by the D4 dopamine receptor leading to neuronal synchronization and attention, and synchrony is impaired in autism. Authors conclude that "redox/methylation hypothesis of autism" is explained by oxidative stress, initiated by environment factors in genetically vulnerable individuals, and leads to impaired methylation and neurological deficits [12].

Recently, it was reported that mold exposure causes neurological injury. When patients who developed symptoms of peripheral neuropathy (i.e., numbness, tingling, tremors, and muscle weakness in the extremities) due to exposer to molds at home had elevated titers of antibodies (immunoglobulin IgA, IgM, and IgG) to neural-specific antigens (myelin basic protein, myelin-associated glycoprotein, ganglioside GM1, sulfatide, myelin oligodendrocyte glycoprotein, alpha-B-crystallin, chondroitin sulfate, tubulin, and neurofilament). Nerve conduction studies revealed mixed sensory-motor polyneuropathy, motor neuropathy, and sensory neuropathy. The authors concluded that exposure to molds in water-damaged buildings increased the risk for development of neural autoantibodies, peripheral neuropathy, and neurophysiologic abnormalities in exposed individuals [13].

In the reported by us clinical venues, all children were living in the unhealthy households during their intrauterine and early life, and the sensitization to molds was confirmed by different physicians. Exposure to a biologically active mold material and fumes can lead to the immunologic shift from normal development and predispose any subsequent activation of the autoimmune mechanisms affecting all systems including developing brain tissues. From the pathogenic point of view these illnesses can be seen to be related to, on one hand autoimmune diseases, and on the other infectious diseases (Picture 1). Early developmental exposure and allergic sensitization to mold spores is not well-studied and, from a diagnostic point, poorly defined entity [14]. New evidence even from bench research and murine experiments demonstrates that molds and mycotoxins are directly and indirectly causing, or attributed to cause, much more morbidity than the two other diseases. In the recent decade, there has been a shift in the focus of immunology from the lymphocyte centered, adaptive immunity towards innate immunity. The archetypal cell in innate immunity is the macrophage although many other cell types participate. Innate immunity relies on a limited number of germline coded receptors for the recognition of pathogens and signs of cellular damage. The focus on innate immunity has opened new paths for the understanding of many chronic inflammatory diseases [15].



Proposed mechanism of neuroimmune interactions in the presence of high levels of sensitizing proteins and environmental toxins during early brain development. Immune system inflammatory responses through neuroglia macrophages with disruption of immune tolerance and normal neuronal network functioning.

To date, there are no guidelines or even suggested protocols for evaluation of children grown in water damaged, unhealthy conditions with extensive mold and allergen presence. As such, pediatricians involved in a care of reported children randomly ordered laboratory and imaging studies mostly to rule our other pathology. A multicenter study investigated the immunological changes in adults exposed to mixed-molds infestation in water-damaged buildings. The authors present data on symptoms; clinical chemistries; abnormalities in pulmonary function; alterations in T, B, and natural killer (NK) cells; the presence of autoantibodies (i.e., antinuclear autoantibodies [ANA], autoantibodies against smooth muscle [ASM], and autoantibodies against central nervous system [CNS] and peripheral nervous system [PNS] myelin). Abnormally high levels of ANA, ASM, and CNS myelin (immunoglobulins [Ig] G, IgM, IgA) and PNS myelin (IgG, IgM, IgA) were found; odds ratios for each were significant at 95% confidence intervals,

showing an increased risk for autoimmunity. The authors conclude that exposure to mixed molds and their associated mycotoxins in water-damaged buildings leads to multiple health problems involving the CNS and the immune system, in addition to pulmonary effects and allergies. Mold exposure also initiates inflammatory processes [16].

Maturation of the immune system, just like nervous system, starts early in fetal life. Lymphocytes of the B series develop in the liver by 9 weeks' gestation and are present in the blood and spleen by 12 weeks. T lymphocytes start to leave the thymus from about 14 weeks' gestation and subsequently cells with helper and suppressor phenotypes are present in the spleen. The relative lack of development of secondary lymphoid tissues in healthy fetuses most probably reflects the lack of antigen stimulus. Newborn plasma contains adult levels of IgG which is acquired across the placenta from the mother. IgA synthesis normally starts in the secretory immune system, about 2-3 weeks after birth. Poor antibody responses by newborns following immunization, especially with bacterial capsular polysaccharides, suggest that newborn immune responses are immature as compared with adults. These characteristics more likely result from a lack of prior antigen stimulation and resulting clonal expansion than from intrinsic lymphocyte suppression [6]. In one of the children a more thorough analysis of lymphocytes was ordered to rule our immunodeficiency. We see high CD3 and CD4 but low CD19. Cell count demonstrates low total white count with neutrophilia and lymphocytosis.

An immune system is actively learning about environmental epitops starting even before birth. The developing fetal naive immune system must learn to recognize future environmental protein and tolerate benign antigens for normal responses. prevents development of autoimmune attack is prevented by the tolerance of self-antigens and is achieved by both deletion of autoreactive T cell clones in the thymus (central tolerance) and by the suppressive influence of CD4+ CD25+ FoxP3+ regulatory T cells (Tregs) in the periphery. While fetal CD4+ T cells have a strong predisposition to differentiate into tolerogenic Tregs that actively promote tolerance to self and non-inherited antigens on chimeric maternal cells that reside in fetal tissues, a crucial transition must occur around birth when an interaction between the tolerogenic fetal system and a defensive aquired immune system for a differentiating capacity between normal and pathogenic to occur [17]. Recent findings show that difference between tolerable and autoreactive T cells is crucial in the development of an autoimmune disease. Development of allergic disease is associated with a more marked Th2- like deviation already at birth, shown as increased levels of macrophage derived chemokines (CCL22) and higher ratios to IP- 10 (CXCL10) and I- TAC (CXCL11) [18, 19].

Up to 80 genera of fungi have been linked to type I allergic disease, and yet, commercial reagents to test for sensitization are available for relatively few species. In terms of asthma, it is important to distinguish between species unable to grow at body temperature and those that can (thermos-tolerant) and thereby have the potential to colonize the respiratory tract [20]. Autoimmunity and abnormal production of inflammatory antibodies are known to affect neurodevelopment due to abnormal, and cause other developmental problems such as low weight gain, predisposition to seizures and learning disabilities. Multiple experimental pulmonary exposures to S. chartarum induced significant metabolic changes in the lungs but not in the plasma. These changes suggest a shift from type 1 inflammation after an acute exposure to type 2 inflammation after multiple exposures to S. chartarum. Eotaxin, vascular endothelial growth factor (VEGF), MIP-1α, MIP-1β, TNF-α, and the IL-8 analogs macrophage inflammatory protein-2 (MIP-2) and keratinocyte chemoattractant (KC), had more dramatic changes in multiple- than in single-dosed mice, and parallel the cytokines that characterize humans with histories of mold exposures versus unexposed control subjects [21].

More research groups confirmed the effect of S. chartarum mold and trichothecene mycotoxins on the pro-inflammatory cytokine response in human macrophages. These mycotoxins strongly enhanced LPS-dependent secretion of IL-1beta and IL-18; triggered the activation of caspase-3, which is an effector caspase of apoptosis. Results indicate that human macrophages sense mycotoxins as a danger signal, which activates inflammatory response through caspase-1, and further enables the secretion of IL-1beta and IL-18 [22, 23].

Harmful exposures to high level of allergenic proteins can cause IgG response (which was documented by abnormal lymphocyte blood test and demonstration of specific IgG antibodies) and abnormal development of immune recognition, which in turn predisposes developing immunity to shift from TH1/TH2 balance required for tolerance to aggressive TH2 (allergic responses) and weak TH1 (bacterial and viral protection) [24].

Fungal exposure to epithelial cells causes production of cytokines, such as IL-25, IL-33, and TSLP, which activate ILC2s and initiate TH2-type differentiation of naive CD4+ T cells. DCs and their cytokines, such as IL-6, IL-23, and IL-12, also drive proliferation and differentiation of CD4+ T cells. TH1 cells activate macrophages through secretion of IFN-γ. TH17 cells produce IL-17 and IL-22, which mediate CXCL8-dependent neutrophil recruitment and production of antimicrobial peptides by epithelial cells, respectively. ILC2s and TH2 cells produce IL-5 and IL-13, which mediate eosinophilic inflammation, goblet cell hyperplasia, and airway remodeling. Effector cells, including macrophages, neutrophils, and eosinophils, use distinct strategies to provide antifungal immunity [25].

One of the most common trigger in asthma development and exacerbations is continuous exposure to allergens of which fungal agents are important factors. There is overwhelming evidence for the presence of fungal sensitization in patients with asthma. The diagnosis of fungal sensitization can be confirmed with skin testing with antigens or measuring specific IgE levels. There is also a strong association between fungal sensitization and severity of asthma. Severe asthma with fungal sensitization is characterized by early onset of disease and high serum levels of interleukin-33. Multiple fungal sensitizations are associated with poor asthma control [26]. Asthma is on the rise in many middle- and lower-income countries. The disease is complex, and its etiology is poorly understood, which explains failure of most treatment strategies. We know that in children, asthma is closely linked to poor lung function in the first 3-years of life, when the lung is still undergoing post-natal alveolarization phase. Epidemiological studies also suggest that environmental factors such as indoor allergens in ear-

ly life play a critical role in the establishment of early wheezing which persists until adulthood [27].

Asthma is associated with multiple neuropsychiatric disorders in children and adults, some of which are anxiety, attention deficit hyperactivity disorder, autism, and depression. Interestingly, the retrospective cohort analysis of 150,827 patients demonstrated that Asthma may be associated with high epilepsy risk, and epilepsy may be associated with high asthma risk among children [28]. Proinflammatory cytokines play neuromodulatory functions, in addition to contributing to aberrant neuronal excitability underlying seizure disorders. Epilepsy and asthma share excitatory factors such as voltage-gated sodium channels, glutamate (i.e., N-methyl-D-aspartic acid), and acetylcholine, as well as inhibitory factors such as voltage-gated potassium channels, γ-aminobutyric acid (gamma-aminobutyric acid [GABA]), glycine, and taurine. One study proposed a pathogenetic mechanism of asthma, similar to that of epilepsy, as a syndrome pertaining to genetically predisposed or inducible membrane hyperexcitability [29, 30].

Immediate remediation of the problem is a strong recommendation in current treatment parameters. The United States Centers for Disease Control and Prevention reported in its June 2006 report, "Mold Prevention Strategies and Possible Health Effects in the Aftermath of Hurricanes and Major Floods", that "excessive exposure to mold-contaminated materials can cause adverse health effects in susceptible persons regardless of the type of mold or the extent of contamination." When mold spores are present in abnormally high quantities, they can present especially hazardous health risks to humans, including allergic reactions or poisoning by mycotoxins, or causing fungal infection (mycosis) [31].

Avoidance of allergen re-exposure reduces the risk of asthma and multi-sensitization to other airborne allergens. Preventive measures may include both exposure to allergens and adjuvant risk/protective factors and pharmacological treatment. These measures may address the general population, children at risk for development of atopic disease (high-risk infants), children with early symptoms of allergic disease or children with chronic disease. Construction remediation aimed at the root cause of moisture sources and combined with a medical/behavioral intervention significantly reduces symptom days and health care use for asthmatic children who live in homes with a documented mold problem [32].

Once occupant-related information has been gathered, a home environmental exposure assessment should be performed focused on identifying the relationships between any identified sources of contaminants and the housing systems, and conditions that may be contributing to exposure. The results and recommendations from this assessment can then be used to guide exposure-reduction efforts by patients and/or their caregivers in an effort to improve disease management.

Allergen avoidance can reduce the need for pharmacological treatment, SIT may have the potential for preventing the development of asthma in children with allergic rhinoconjunctivitis, and it may be possible to interfere with the natural course of allergic diseases [33].

Conclusion

This case report study is aimed toward alerting physicians to an unhealthy indoor environment conditions as a probable causative factor in the investigation of atypical neurologic presentations in early childhood. Novel opportunities, such as sublingual immunotherapy, should be considered in treatment of children who develop allergic sensitization and neurological issues, as an option to restore normal development. Allergen avoidance and remediation of unhealthy living conditions should be a sound recommendation if an indoor air quality is found unhealthy by an environmental report. More research is needed to evaluate specific mechanisms involved in early immune system development and interaction of sensitized immune cells with neuroglia and brain development. We emphasize clinical implications unhealthy living conditions on the intrauterine development and very early life, when a skewed immune response triggered by a sensitizing exposure may negatively affect the future development and functioning of a child. Neurodevelopmental complication in children with known history of unhealthy home environment should be investigated by clinicians. We suggest considering damp conditions, allergen sensitization, VOC toxic effects from decaying buildings when evaluating an atypical childhood epilepsy, autism spectrum of disorders, and behavioral disorders. Treatment recommendations should include current published standards on immediate home remediation, relocation of affected family and allergen avoidance. When allergy is confirmed, an allergen desensitization such as sublingual immunotherapy, should be attempted to recover a normal neuroimmune signaling and normal neurodevelopment. As there is a significant lack of published guidelines, further multidisciplinary research of etiology and pathophysiological mechanisms is needed. Clinicians could significantly benefit from future clinical interventional trials and treatment guidelines in a management of children exposed to mold and unhealthy homes.

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