VIRUS & ASTHMA

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ROLE OF VIRUSES IN WHEEZING IN INFANTS AND YOUNG CHILDREN

Viruses are a common trigger of wheezing illness in children, and virus-induced wheezing represents a heterogeneous group of illnesses including bronchiolitis, asthma exacerbations, and croup

Viral respiratory tract infections

infants and young children : Wheezing with RSV and RV predispose to develop asthma later in life

enteroviruses, bocaviruses, coronaviruses,

parainfluenza, influenza, humanmetapneumoviruses (hMPV), and adenoviruses

Risk Factors?

over two yr with wheezing by viral infection are more likely than those without virus-induced to have features that are associated with a predisposition to asthma including:

1- Elevated IgE

2- Sensitization to inhalant allergens

3- Eosinophilic inflammation

4- Maternal history of asthma

Host factors

asthmatic pt not contracting virus compared healthy

long duration of sympt and more severe viral-illness

Host factors likely play a role in this exaggerated

immune response to viral infections in asthma.

Lung function & virus

*prospective 1246 children relationship initial lung function and the development wheezing the first year infants with reduced lung function were more likely to develop asthma later

*children with prematurity and lower lung function in infancy are at increased risk of RSV-induced lower respiratory illness, recurrent virus-induced wheezing, and asthma

The Copenhagen Prospective Studies

responses to bacterial and viral pathogens

during infancy may further modulate future

asthma risk

How viruses impact asthma

1- viral infections and subsequent asthma

2- the relationships between host genetics and viral infections

3-respiratory viral infections to patterns of immune development

4- the impact of environment on the severity of viral infections

5-viral genome influences host immune respon to viral infections

Respiratory viruses interact with allergic sensitization and other microbes to promote development of asthma via a number of mechanisms including

1- increased recruitment of inflammatory cells

2- promotion of cytokine production

3- enhancement of allergic inflammation

4- augmented airways hyperresponsiveness

Viral Factors

it is unclear whether certain viral respiratory infections play a role in asthma inception or if wheezing with these infections is a predictor of childhood asthma

influenza and RSV

cytopathic damage to airway epithelium proinflammatory :

thymic stromal lymphopoietin (TSLP), IL 25, and IL-33.

propagates eosinophilia and stimulates the release of cytokines that promote asthma and atopic disease (IL-4, IL-5, IL-13) .

RSV

The causal effect early-life RSV on develop asthma

unclear

studies clearly RSV increased risk of asthma.

children persistent asthma or that develop asthma

after RSV have asthma risk factors:

maternal history of asthma and elevated IgE levels

RSV

premature, 146 palivizumab and 171 untreated, RSV prophylaxis

decreased the risk of recurrent wheezing in child w/o atopy but had

no effect in atopic

prevention of RSV infec is an important factor if you are not at risk for

atopy but that FH of atopy overrides any influence of RSV prophylaxis

hMPV

young children hospitalized with hMPV lower respiratory tract infections have an increased risk of developing asthma at age five years .

increased risk of asthma development was similar to RSV

Rhinovirus

may not damage the epithelium directly but rather interact with macrophages, T cells, or mast cells to stimulate allergic airway inflammation and modulate the host response to allergens, irritants, and the environment

RV

RV-A, RV-B, and RV-C serotypes

1- few cytopathic effects on airway epithelium

2- induce a significant airway inflammatory immune response

3- impair the antiviral interferon (IFN) response during infections

COVID-19; SARS-CoV-2

Asthma does not appear to be a strong risk factor for acquiring coronavirus disease 2019 or to increase the risk of more severe disease or death for the majority of patients

the relationships between host genetics and viral infections

The clinical manifestations of a viral infection in

the respiratory tract result from a complex

interplay of the host, the environment, and the virus

respiratory viral infections to patterns of immune development

To make comparisons between different

immune responses elicited by diverse viruses,

the host and the environmental conditions must

be held constant to prevent the introduction of

confounding factors.

1- human cell lines for in vitr infection studies

2- infection of genetically identical animals

such as mice, housed in the same environment

3- the use of a standard viral inoculum

Determining the effect of specific genes within a virus requires that all other viral genes be identical. Such studies have begun but are still relatively new

THE VIRAL GENOME

Three RSV strains : A2, line 19, and Long RSV

A2 : a predominant IFN-g immune resp, no product of the TH2 cytokine IL-13 in the lung, an absence of airway mucus, and no AR to methacholine.

Long : did not result in host IL-13 production in the lung, nor was there airway mucus

line 19 : produce IL-13, decreased IFN-g level compared with that in A2 infection, airway mucus, and heightened AR

THE VIRAL GENOME

provide knowledge of the unique components of the viral genome that contribute to specific pathogenic features but may also assist in vaccine and therapeutic strategies aimed at the proteins responsible for specific disease characteristics

HOST GENETICS AND VIRAL RESPIRATORY INFECTIONS

Polymorphisms in several antiviral and innate immune genes have been linked to susceptibility to respiratory viruses, infection severity, and virus-induced asthma exacerbations, and they have been replicated across multip cohorts.These genesinclude

STAT4, JAK2, MX1, VDR, DDX58, and EIF2AK2.

Genetic

Genotypic variants at the 17q21 locus are associated with both RV wheezing illnesses in early childhood and the development of asthma in these children.

In addition, variants in the gene encoding cadherin-related family member 3 (CDHR3) may be linked to increasing wheezing illnesses in children by mediating increased RV-C entry into host cells

Atopy and viral infections ?

allergic sens in the 1 yr of life is the initial event

that interacts with viral infections, particularly

RV, to promote the development of asthma in

children

Atopy and viral infections

TH2 inflammation can inhibit type I and III interferon antiviral responses to RV infections which may increase susceptibility to more severe RV infections.

In contrast, however, several human studies have demonstrated increased interferon signatures in asthmatic children with virus infections, as well as in adults with severe asthma

Interferon & asthma?

that early-life exacerbation-prone asthma

was correlated with low interferon signatures, whereas the highest interferon signatures were associated with later-onset asthma.

Atopy and Viral Infections

A key question, however, is whether underlying TH2 inflammation or RV-associated wheezing comes first.

A prospective :

suggesting that allergic sensitization may lead to more severe RV illnesses and development of asthma

Future perspectives

These genetic associations among respiratory virus susceptibility, infection severity, and subsequent asthma risk may prove to be important to risk-stratify populations and may potentially provide new therapeutic targets for reducing illness severity and subsequent risk

ENVIRONMENTAL FACTORS

From birth through the school years, children are frequently exposed to a variety of respiratory pathogens, allergens, microbes, and airway irritants.

The pathogenic or beneficial effects of these exposures and their interactions remain the focus of research to develop new interventions and preventive therapies

Risk factors for acute wheezing

1- exposure to cigarette smoke, particularly maternal

2- persistently reduced lung function

3- allergic sensitizations

ENVIRONMENTAL FACTORS

flares of wheezing caused by RV are more strongly linked to persistent wheezing and the development of asthma, especially in children who are sensitized to allergens at an early Age

Allergic inflammation

1- antiviral and increase susceptibility to and severity of viral respiratory illnesses.
2- modify the relationship between microbial colonization and respiratory outcomes.
3- preschool children pathogen-dominated microbiomes,sensitized increased risk for chronic asthma whereas nonsensitized children were likely to have transient wheeze

Future perspectives

altering TH2 skewing in early life

1- blocking IgE

2- altering microbial exposures

decreasing TH2 inflammation in early life may enhancing antiviral responses.

BACTERIAL COLONIZATION DURING VIRAL URI

bacteria present in the airway during viral

illnesses may contribute to both illness severity

and long-term sequelae

Looking to the future

Ab to treat secondary bacterial pathogens or azithromycin to reduce wheezing following virus infection also deserve further study, determine whether the vitamin D, probiotics, and dietary modifications (eg, fish oil) will have benefits.

THE INFLUENCE OF THE GUT MICROBIOME

most abundant microbial environment in the human

short-chain fatty acids regulate immune responses.

the frequent use of antibiotics and the consumption of a high-sugar, low-fiber diet, loss of metabolic capabilities and predisposes infants to both development of AD and increased viral infections

gut microbiome & asthma

the mechanisms remain unclear. The most popular theory to explain these observations is that colonization with certain gut bacteria have a direct anti-inflammatory effect on the respiratory tract, decreasing the likelihood of airway hyperreactivity

Viruses and the microbiome

RV alter the airway microbiome, with increased detection of S.pneumoniae, Moraxella catarrhalis, and H. Infl in children with and without asthma .

This coalescing of antimicrobial immune responses was associated with increased respiratory symptoms

Future perspectives

the gut microbiome can influence maturation of the immune system in viral defense and therefore the development of asthma.

Future therapies look to a role of probiotics for the prevention and treatment of allergic disorders

PRIMARY PREVENTION

Early-life respiratory infections are significant determinants of childhood asthma.

In young toddlers, prevention of severe RSV bronchiolitis may reduce the risk of episodic wheeze and/or asthma development.

In preterm palivizumab treatment during the RSV season resulted in a 73% reduction in the number of wheezing days during 1 year of life

Asthma prevention

early infections cannot prevented, attenuation of immune/inflammatory processes during these infections

azithromycin treatment for 2 weeks during acute RSV bronchiolitis reduced the likelihood of development of recurrent wheeze during the subsequent year.

Azithromycin: 1- anti-inflammatory properties
2- effects on the airway microbiome.

Antibiotics

Current guidelines do not recommend the use of antibiotic treatment for episodes of asthma-like symptoms in children, yet they are commonly used.

VIT D3

maternal vitamin D deficiency to childhood asthma maternal vitamin D supplementation (2400 IU per day or 4000 IU per day) during pregnancy would prevent asthma and/or recurrent wheeze in their children

VIT D3?

significant (25%) reduction in asthma and/or recurrent wheeze risk during the first 3 years of life.

beneficial effects of vitamin D may be related to enhancement of in utero lung growth and development and promotion of antimicrobial effects, thereby reducing early-life respiratory infections and/or providing immune modulation effects

Omega-3

have anti-inflammatory effects. high-dose omega-3 fatty acid supplementation (2.4 g daily) to pregnant women, beginning at 24 week of gestation, resulted in a 30% reduction in relative risk of persistent wheeze or asthma at age 3 years NEVERTHELES it is high-dose omega-3 safety issues?

omalizumab

1- decreased frequency of RV illnesses

2- decreased duration of RV infection

3- reduced peak RV shedding

4- reduced expression of FcεRIa on pDCs