Acute rotavirus infection causes significant activation of the IL-33/IL-13 axis

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ABSTRACT

Aim: Overactivation of the IL-33/IL-13 axis is the main step in initializing allergic inflammation and promoting allergic diseases. Data on viral pathogens as risk factors for subsequent allergic disease are contradictory. The strongest associations have been made between upper respiratory tract virus infections and asthma. Intestinal viral infections also activate IL-33 and IL-13 as part of the innate antiviral response. The aim of this study was to test whether there are differences in IL-13 and IL-33 concentrations in pediatric patients with acute rotavirus- and norovirus infections and healthy controls.

Material and Methods: Forty children with acute rotavirus, 27 with acute norovirus intestinal infections and 17 control children were enrolled in this study. Blood IL-33 and IL-13 detection was performed with enzyme-linked immunosorbent assays (ELISAs).

Results: Acute rotavirus infection caused a significant elevation in IL-33 and IL-13 compared to acute norovirus infection (63.85 pg/ml vs. 0, P = 0.0026, and 94.24 pg/ml vs. 0.88 pg/ml, P = 0.0003, respectively) and healthy controls (63.85 pg/ml vs. 9.89 pg/ml, P = 0.0018, and 94.24 pg/ml vs. 0.14 pg/ml, P < 0.0001, respectively). There was no significant difference in IL-33 and IL-13 concentrations between the acute norovirus group and healthy controls (0 vs. 9.89 pg/ml, P = 0.8276 and 0.88 pg/ml vs. 0.14 pg/ml, P = 0.1652, respectively).

Conclusion: Acute rotavirus infection causes a significant elevation in IL-33 and IL-13, compared to norovirus and healthy control children.

KEY WORDS
interleukin-13 – interleukin-33 – Norovirus – Rotavirus

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INTRODUCTION

The prevalence of childhood atopic diseases continues to rise, especially in developed countries. Atopic diseases are multifactorial, and their main pathogenic feature is – an altered immune response towards environmental antigens [1]. There has been debate about the possible triggering factors. Studies show that dysregulation of the dominant type of cytokine response and its magnitude leads to overactivation of immune cells, which in turn impacts the occurrence, exacerbation, or severity of a disease [2]. Researchers take particular interest in viral infections. The term "post-viral atopic cycle" has been proposed. The strongest associations were found between viral respiratory infections and the development or exacerbation of asthma [3]. Data regarding association between acute intestinal infections and atopic diseases are inconclusive; however, evidence is growing that acute gastrointestinal viral infections are a possible trigger for upregulating the Th2 immune response and promoting Th2- dominant diseases. Pan et al. showed that early-life gastroenteritis is associated with increased rates of asthma, allergic rhinitis, and atopic dermatitis [4]. Thomson et al. demonstrated that recurrent gastroenteritis in early childhood is associated with subsequent development of asthma [5]. Reimerink et al. showed that rotavirus infection in the first year of life is a risk factor for wheezing. Children seropositive for rotavirus at age 1 have an increased risk for asthma and wheezing, and former norovirus infection is associated with a decreased risk for asthma and wheezing [6].

Recent evidence suggests that the IL-33/IL-13 axis is a key pathway in driving viral infections and virus-induced exacerbations of allergic diseases [7]. Induction of the IL-33/IL-13 axis following viral infection has been shown to play the main role in promoting airway hyperresponsiveness – the main feature of wheezing and asthma [8]. Interleukin-33 (IL-33) is a member of the interleukin-1 family of cytokines and is found in the nuclei of various tissues and immune cells in the human body. IL-33 is highly expressed in barrier tissues, that are exposed to the environment (e.g., skin, gut, lungs), and these tissues are considered the major sources of IL-33 in the human body [9].

Extracellular IL-33 can be detected following cellular damage or stress due to infection or allergen exposure [10]. Data show that certain viral strains induce IL-33 overexpression in epithelial cells [11]. IL-33 is a Th2-type immune response inducer and is a strong activator of IL-13 synthesis and secretion. The biological role of IL-13 is widely recognized in the pathogenesis of allergic diseases and helminth infections. However, studies show that IL-13 biological functions are more complex and that it is involved in pathogenesis in inflammatory conditions [12]. IL-13 can be produced by activated type 2 innate lymphoid cells (ILC2), Th2 cells, mast cells, macrophages, basophils, eosinophils, B-cells, and NK cells [13]. IL-13 production is stimulated by gut epithelium-derived signals, such as IL-33; therefore, IL-13 is crucial in mucosal immune responses [14]. Elevation of IL-13 blood concentration has multiple biological effects on distant organs and cells. In the lungs, IL-13 is a key activator of mucus-secreting cell hyperplasia, airway hyperresponsiveness, and remodeling of the airways, which leads to bronchial obstruction and airflow limitations [15]. In the intestine, IL-13 promotes intestinal stem cell differentiation, increases intestinal permeability, and causes goblet cell hyperplasia, which changes mucosal tissue architecture: promoting villous atrophy, crypt hyperplasia, and thickening of the *muscularis externa* [16]. In the skin, IL-13 activates inflammatory cells to secrete chemokines and cytokines, disrupts skin barrier integrity by downregulating the expression of structural proteins and lipids, promotes fibrosis, and stimulates peripheral itch-sensory neurons [17]. IL-13 is believed to be the main crosstalk molecule between distant mucosal sites. Since IL-13 release can be activated by injured or inflamed intestinal epithelium it is vitally important in innate immune responses and defense mechanisms in the intestinal mucosa. Studies propose, that IL-13 might be a key element in the pathogenesis of atopic march [18].

Investigations on the clinical significance of IL-33-IL-13 overactivation are underway. However, according to Xu et al., significant IL-33 elevation is correlated with IL-13 elevation and increased accumulation of ILC2s in the lungs after severe trauma [19]. *Ascaris lumbricoides*-infected mice show a robust Th2-type cytokine response, especially in IL-13, and the infection directly induces severe allergic airway disease [20]. It has been noted that IL-13 concentration depends on the pathophysiology of the pathogen. Lukacz et al. demonstrated, that different respiratory syncytial virus subgroup strains provoke significantly different IL-13 responses and therefore differ in airway hyperreactivity in mice [21]. Therefore, IL-33-IL-13 axis overactivation might be a risk factor for the activation of allergic-type inflammation and allergic complications.

MATERIAL AND METHODS

2.1. Study population and ethical considerations

A total of 84 children were recruited in the study. Sixty-seven children with acute intestinal infection and no history of allergic diseases were hospitalized in the Children's Infectious Disease Department. Sixty percent (n = 40) had acute rotavirus infection and comprised the rotavirus test group. Forty percent (n = 27) had acute norovirus infection and comprised the norovirus test group. The rotavirus test group comprised 50% (n = 20) boys and 50% (n = 20) girls. The mean age was 34.4 ± 22.6 months. The norovirus test group comprised of 30% (n = 8) boys and 70% (n = 19) girls. The mean age was 25.6 ± 20.3 months. Seventeen children with no signs of current infection or any history of chronic diseases comprised the control group. Statistically, there was no difference between the three groups in age and sex. Ethics committee approval for the study was obtained. Participants' parents or legal guardians expressed approval for the children's participation in the study by providing written informed consent.

2.2. Sample collection and laboratory analysis

Venous blood samples were obtained from all test and control children. The samples were collected as part of routine clinical practice. Venous samples were incubated at room temperature to allow complete formation of a clot, after which the samples were centrifuged (1200 x g 10 min, 4 °C) and the separated serum was transferred to new tubes and was frozen at 80°C for further IL-13 and IL-33 testing.

2.3. IL-33 and IL-13 measurements

Frozen serum samples were completely defrosted prior to testing. IL-33 and IL-13 detection was performed using a human IL-33 ELISA kit (Elabscience, China), and human IL-13 ELISA kit (Elabscience, China). A quantitative assessment of cytokines was made using Sandwich-ELISA method. Micro-ELISA plates were pre-coated with an antibody specific to IL-33/IL-13. Standards and samples were added to the appropriate micro-ELISA plate wells and combined to the specific antibody. Free components were removed by washing. A biotinylated detection antibody, specific for IL-33/IL-13 and Avidin-Horseradish Peroxidase (HRP) conjugate was added to each micro plate well successively and incubated. Free components were removed by washing. A substrate solution was added to each well. Wells, that contain IL-33/IL-13 biotinylated detection antibody and Avidin-HRP conjugate appeared blue in color. The enzyme-substrate reaction was terminated by adding a sulphuric acid solution, which changed color into yellow. The optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value was proportional to the concentration of IL-33/IL-13, which was calculated using a standard curve.

Table 1. Differences in IL-33 and IL-13 concentrations between the test and control groups

	Rotavirus group	Norovirus group	Control group	P value*		
				Rotavirus gr. vs. Norovirus gr.	Rotavirus gr. vs. Control gr.	Norovirus gr. vs. Control gr.
IL-33	63.85 (0 – 5814.62)	0 (0 – 641.49)	9.89 (0 – 423.94)	0.0026	0.0018	0.8276
IL-13	94.23 (0 – 540.52)	0.88 (0 – 252.89)	0.14 (0 – 37.842)	0.0003	<0.0001	0.1652

**P value for the Mann-Whitney U test between the test groups.*

According to the manufacturer, the upper detection range for IL-33 and IL-13 was 1000 pg/ml. Samples with higher concentrations were diluted following standard laboratory procedures.

2.4. Data management and statistical analysis

MS Office Excel, and MedCalc software were used for data management and statistical analysis. Nonparametric data are expressed as the median and range. The Mann-Whitney U test was used to compare two groups of variables. A relationship between the two variables was defined using Spearman's rank correlation coefficient. Categorical data are expressed as numbers and percentages, and differences were determined using the chi-Square test. Differences between the groups were considered significant when $P < 0.05$.

RESULTS

Children in the rotavirus group presented with significantly higher IL-33 (63.85 pg/ml. vs. 0, $P = 0.0026$) and IL-13 (94.24 pg/ml. vs. 0.88 pg/ml, $P = 0.0003$) levels compared to those in the norovirus group. See Table 1. The IL-33 and IL-13 levels were also significantly different compared to the control group (63.85 pg/ml. vs. 9.89 pg/ml, $P = 0.0018$, 94.24 pg/ml vs. 0.14, $P < 0.0001$, respectively). The IL-33 and IL-13 levels in the norovirus test group were low and did not differ from those in the control croup (0 vs. 9.89 pg/ml, $P = 0.8276$ and 0.88 pg/ml vs. 0.14 pg/ml, $P = 0.1652$, respectively).

A strong positive correlation between IL-33 and IL-13 values was observed in the rotavirus group ($r = 0.621$, $P = 0.0002$). A weak positive correlation between the two variables was detected in the norovirus group, but the results were not statistically significant ($r = 0.045$, $P = 0.8388$).

DISCUSSION

IL-33 and IL-13 are critical in mucosal immune responses. Overactivation of the IL-33-IL-13 axis during viral infection leads to mucosal hyperreactivity and changes, linked to allergic diseases and consistent with dominant systemic Th2 inflammation [1]. The exact mechanisms of this crosstalk between mucosal barrier surfaces and the immune system are not exactly clear; however, IL-33 and IL-13 are crucial to the process [22]. Exogenous IL-33 promotes Th2 immune inflammation. Resende et al. demonstrated that elevated blood IL-33 concentration following *Schistosoma mansoni* infection is positively correlated with subsequent allergic reactivity [23]. Experimental studies have showed that chronic IL-13 exposure leads to a goblet cell hyperplasia and decreased ciliated cell numbers in the paediatric bronchial epithelium cell cultures, which is characteristic of asthma [24]. Studies also demonstrate, that IL-13 overactivation not only induces inflammatory and remodeling responses in the lungs but also promotes certain gene rearrangements and possesses a long-term pathological effect [25]. Taken together, IL-33-IL-13 overactivation during childhood might be considered a risk factor for a subsequent allergic disease.

According to this study, children with acute rotavirus infection had significantly higher IL-33 and IL-13 concentrations than the norovirus group and healthy children. Data concerning human studies with rotaviruses and noroviruses are lacking; however, it is known that rotaviruses directly infect and disrupt intestinal enterocytes [26]. Noroviruses, on the other hand, bind to carbohydrates expressed on gut enterocytes or microbiota, then are transcytosed across the intestinal epithelial barrier and gain access to their target – intestinal immune cells [27]. Chen et al. demonstrated that rotavirus infections are more severe and cause significantly reduced microbiota diversity than norovirus infections [28]. Human rotaviruses cause a more severe acute gastroenteritis clinical symptoms than noroviruses in terms of frequency and duration of vomiting, fever severity and abdominal pain [29]. Rotaviruses cause more vigorous cellular disruption than other enteric viruses. However, experimental murine models demonstrate that even subclinical norovirus infections cause epithelial barrier disruption [30]. The main sources of extracellular IL-33 in the intestine are intestinal epithelial cells and their damage [31]. Enlady et al. demonstrated that

intestinal injury biomarkers are higher in the rotavirus group than in other intestinal virus groups [32]. The IL-33 blood concentration is high in cases when tissue integrity is disrupted [33]. Therefore, significant IL-33 elevation in the rotavirus group that we observed must be connected to rotavirus pathophysiology and reflect intestinal epithelial cell damage. Duan et al. found that a significant increase in IL-33 concentration is associated with colonic tissue destruction in an experimental murine colitis model [34]. IL-33 elevation in response to hyperoxia is positively correlated with IL-13 concentration and is associated with asthma-like features in premature infants [35]. According to Halat et al., IL-33 concentration is increased in polytraumatised patients and it is associated with subsequent pulmonary complications [33].

The main IL-13-producing cells in the intestine are NK cells, T-lymphocytes, and ILCs [13]. IL-13 secretion is activated in response to intestinal cellular damage [36]. Intestinal viruses activate mucosal NK cells and promote IL-13 secretion as a part of the innate immune response. IL-33 is a strong IL-13 secretion inducer. Zhu et al. showed that exogenous IL-33 significantly increases IL-13 production in a murine model of experimental acute colitis [37]. Our study shows a positive correlation between IL-33 and IL-13 concentrations. Kaur et al. detected a positive correlation between increased IL-33 expression and IL-13 secretion and the presence of airway hyperresponsiveness [38]. Studies have also demonstrated that significant IL-33 elevation is associated with an increase in Th2-type cytokines in an experimental murine model of colitis [34]. We found that IL-13 was higher in the rotavirus group. Intestinal mucosal responses to rotavirus infection take part in shaping the immune response towards pathogens. Data show that rotavirus promotes intestinal epithelial cell apoptosis and greatly increases intestinal epithelial cell turnover [39]. Pronounced shedding and increased loss of mature intestinal epithelial cells provide signals for the induction of proliferation. IL-13 elevation is essential in myocardial remodeling following myocardial infection [40]. During intestinal barrier breach with increased intestinal cellular disruption, increased IL-33 promotes IL-13 secretion [31]. According to Vorobjova et al., a significant elevation of IL-13 is correlated with small bowel mucosa damage in children with celiac disease [41].

IL-13 secretion during infection is affected by multiple factors, including the pathogen itself. H. Dixon et al. demonstrated that secreted IL-13 concentration varies depending on different helminth subspecies [42]. E. A. Pearson et al. showed no changes in IL-13 during acute norovirus in an experimental murine norovirus model [43]. Our study showed no difference in IL-13 concentration between acute norovirus infection and control children, but there was a significant increase in the rotavirus subgroup. According to M. Parra et al., rotavirus-specific T-cells produce low levels of IL-13 [44]. However, rotavirus-specific T-cells are not the only cells that produce IL-13. Jaimes et al. reported that children with rotavirus diarrhea had fewer virus-specific IL-13 secreting cells than adults [45]. However, only a small percentage of rotavirus-specific cells are circulating in the blood [46]. IL-13 acts in mucosal immune responses. There are limited data about the intestinal mucosal capacity to promote IL-13 responses. An experimental murine model showed that IL-13 secretion is induced in response to intestinal mucosa damage caused by irradiation [47]. Huang et al., demonstrated that IL-13 overstimulation provokes allergic pulmonary reactions in experimental murine enterovirus infection [48]. According to their data, mucous metaplasia and IL-13 hyperproduction last at least one month after infection, and late-phase side effects may provide a link to atopy [49, 50].

This study has some limitations, first, there was a limited number of test and control children; second, there was no follow-up of the test groups.

CONCLUSIONS

Taken together obtained results indicate that childhood rotavirus infection is a risk factor for overactivation of IL-33 and IL-13 and promotion of Th2-type inflammation compared to norovirus infection. Childhood rotavirus infection might be a risk factor for the development of subsequent allergic diseases, but further research is still needed.

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