Immunotherapy Duration and Risk of Psychosocial Emotion and Risk of Attention Deficit Hyperactivity Disorder Prevalence and Relation in Allergic Rhinitis Children

Dinda Anes Tunjungsari[1], Anang Endaryanto[2], Ahmad Suryawan[3], Ariyanto Harsono[2], Zahrah Hikmah[2], Azwin Mengindra Putera[2]

[1]Resident in Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia, [2]Lecturer and Consultant in Allergy Immunology Division Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia, [3]Lecturer and Consultant in Growth and Development Division Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital, Surabaya, Indonesia

Abstract

Background: Allergic rhinitis (AR) is the most common chronic disease in children. Allergic symptoms affect daily activities and increase risk of psychosocial emotion and attention deficit hyperactivity disorder (ADHD). Immunotherapy has been proven in improving AR symptoms

Objective: To identify prevalence of the risk of psychosocial emotion disorder and ADHD and its relation with immunotherapy duration in AR children.

Methods: A cross-sectional study was held in AR children aged 4-18 years at Allergy Immunology Outpatient Clinic, Dr. Soetomo Hospital, during March 2017. Immunotherapy duration categorized into 0-6 months, 6 months-1 year, 1-2 years, 2-3 years. Psychosocial emotion disorder risk assessed using Pediatric Symptoms Checklist 17 (PSC-17), scored into four different subscales: Internalizing, Externalizing, Attention, and Total Score. ADHD risk was assessed using Abbreviated Conner's Rating Scale (ACRS). Statistical analysis using One-Way ANOVA and Eta test, with a value of $p< 0.05$ considered as significant.

Results: Total of 37 children included. Based on immunotherapy duration 0-6 months, 6 months-1 year, 1-2 years, and 2-3 years, prevalence risk of ADHD are 20.6%, 15.4%, 12.5%, and 12.5%, and prevalence of psychosocial emotion disorder risk are only in immunotherapy duration 6 months-1 year 12.5%. There were no correlation between immunotherapy duration with risk of psychosocial emotion disorder ($p = 0.945$) and significantly correlated to ADHD ($p = 0.049$, $r = 0.326$).

Conclusion: Prevalence risk of ADHD decrease as the immunotherapy duration increase and immunotherapy duration weakly correlated with risk of ADHD.

Keywords: *allergic rhinitis,children, immunotherapy duration, PSC-17, ACRS.*

Corresponding author:
Dinda Anes Tunjungsari,
Department of Child Health, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Hospital. Jl. Mayjen Prof. Dr. Moestopo No. 47, Airlangga, Surabaya, East Java, Indonesia, +6281334055577, mail: anes.dnd@gmail.com

Introduction

Allergic rhinitis is the most common chronic disease in children, achieved 40% of the general population. Comprehensive management include education, allergen avoidance, pharmacotherapy, and immunotherapy [1]. Immunotherapy have been proven as an effective therapy either for intermittent or persistent allergic rhinitis. It

takes 3 to5 years to complete immunotherapy, and needs minimum 6 months to achieve maintenance dose [2]. As a house dust mite induced allergic rhinitis management, it provides early effects and long-term effects in reducing symptoms and treatment needs, as well as reducing further hyper-responsiveness [3, 4].

Psychosocial emotion disorder believed as morbidity in children, account for 14-20% school and 13% pre-school aged children. The risk increase 2-3 fold higher for children with low socioeconomic status, single parent, or mentally disorder parent. It could be measured using *Pediatric Symptom Checklist* (PSC), which recommended as psychosocial screening for children in primary healthcare [5, 6]. Prevalence of psychosocial and behavioral disorder in allergic rhinitis children are 24,4%[7]. Attention deficit and hyperactivity disorder in children could be measured using Abbreviated Conner's Rating Scale. Prevalence of attention deficit and hyperactivity disorder in allergic rhinitis children are higher than general population, which are 1% vs 0,5% [8].

Allergic rhinitis symptoms could significantly affect quality of life, including physical function, social function, and mental health. The symptoms bring limitation to daily activities, moreover physical and emotional [1]. Administration of immunotherapy effective in reducing symptoms, therefore the risk of psychosocial emotion and risk of attention deficit and hyperactivity disorder will decrease [3].

The aim of our study is to analyze the prevalence and relation of risk of psychosocial emotion and risk of attention deficit and hyperactivity disorder with immunotherapy duration in allergic rhinitis children.

Methods and Materials

This study was a cross-sectional study. The study were conducted in Pediatric Allergy Immunology Oupatient Clinic during March 2017. It was carried out on 4-18 years old allergic rhinitis children, who administered subcutaneous immunotherapy, and parent signed agreement to join the research were included. The patients were excluded if they had history of psychosocial emotion disorder, or attention deficit and hyperactivity disorder (ADHD), or neurological disorder, or incomplete medical records. Comprehensive informed consent was obtained from a legal representative of the patient. Patients characteristic including gender, age, family history of atopic disease, immunotherapy duration, risk of psychosocial emotion disorder (internalizing, externalizing, attention, and total score), and risk of ADHD. Immunotherapy duration categorized into 0-6 months, 6 months-1 year, 1-2 years, 2-3 years. SPSS ver. 19.0 was used for statistical analysis. One-Way ANOVA was applied to analyze data comparison between groups. Eta test was used to assess the correlation of immunotherapy duration to risk of psychosocial emotion disorder and risk of ADHD. Statistical significance was considered with p-value of <0.05.

Risk of psychosocial emotion disorder

Risk of psychosocial emotion disorder was assessed using Pediatric Symptoms Checklist 17 (PSC-17), scored into four different subscales: Internalizing, Externalizing, Attention, and Total Score. Risk of psychosocial emotion disorder internalizing aspect if internalizing score ≥ 5, externalizing aspect if externalizing score ≥ 7, attention aspect if attention score ≥ 7. Risk of psychosocial emotion disorder were assessed if total score of PSC-17 ≥ 15.

Risk of Attention Deficit and Hyperactivity Disorder

Risk of ADHD was evaluated using Abbreviated Conner's Rating Scale (ACRS), which total score ≥ 13 assessed as having risk of ADHD.

Result

The study was participated by 37 patients. Age range of patients were 4 to 14 years old, median 7 and mean 7.14 ±2.3 years old. According to skin prick test result, all patients allergic to house dust mite. Most of them, 89% have combination of house dust mite, pet, and food allergy (Table 1).

Table 1. Patient characteristics

Characteristics	**n=37 (%)**
Gender	
· Male	20 (54.1)
· Female	17 (45.9)
Age, median (years)	7 (4-14)
Family history of atopic disease	
· Yes	30 (81.1)
· No	7 (18.9)
Allergen	
· House dust mite, pet, food	33 (89.2)
· House dust mite, pet	0 (0.0)
· House dust mite, food	3 (8.1)
· House dust mite	1 (2.7)
Immunotherapy duration	3 (8.1)
· 0 - 6 months	8 (21.6)
· 6 months - 1 year	10 (27.0)
· 1 - 2 years	9 (24.3)
· 2 - 3 years	
Allergic rhinitis based on therapy	
· Mild intermittent	7 (18.9)
· Moderate-severe intermittent	6 (16.2)
· Mild-moderate persistent	8 (21.6)
· Severe persistent	16 (43.2)
Risk of psychosocial emotion disorder	
· Internalizing	5 (13.5)
· Externalizing	1 (2.7)
· Attention	1 (2.7)
· Total	2 (5.4)
Risk of ADHD	9 (24.3)

Prevalence of the risk of psychosocial emotion disorder and risk of ADHD were categorized based on immunotherapy duration. Risk of psychosocial emotion and risk of ADHD decreased gradually by number, as the immunotherapy duration increased. However, only risk of ADHD which consistently decreased, as the immunotherapy duration increased (Table 2).

Table 2. Prevalence of the risk of psychosocial emotion disorder and risk of ADHD based on immunotherapy duration

Immunotherapy duration	n (disorder risk prevalence)				
	Psychosocial emotion				ADHD
	Internalizing aspect	Externalizing aspect	Attention aspect	Total score	
0 -6 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (67.7)
6 months - 1 year	1 (12.5)	1 (12.5)	0 (0.0)	1 (12.5)	3 (37.5)
1 - 2 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)
2 - 3 years	3 (67.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)

There was significant relation between immunotherapy duration and risk of ADHD (p = 0.049), weak correlation (r = 0.326) (Table 3).

Table 3: Relation of immunotherapy duration with risk of psychosocial emotion and risk of ADHD in allergic rhinitis children

		n	Immunotherapy duration (mean), days	p
Risk of psychosocial emotion disorder	Internalizing aspect			0.283
	· Yes	5	844.2	
	· No	32	647.7	
	Externalizing aspect			0.267
	· Yes	1	258.0	
	· No	36	685.8	
	Attention aspect			0.227
	· Yes	1	1127.0	
	· No	36	661.7	
	Total score			0.945
	· Yes	2	692.5	
	· No	35	673.2	
Risk of ADHD				0.049
· Yes		9	461.0	
· No		28	742.8	

Discussion

Pediatric Symptom Checklist-17 were created to evaluate children psychosocial function. This tool is a reliable indicator, which clinical judgement are needed on its utilization [6]. Consist of three aspects, internalizing, externalizing, and attention. Total score of PSC-17 beneficial for general psychosocial function assessment in children [9]. Prevalence of psychosocial emotion disorder internalizing aspect in allergic rhinitis children were 24% (OR 2, CI 95%, 1,6-4,4). Increase to 31% in persistent rhinitis, 32% in multiple atopic disease, and 36% in allergic rhinitis children with another atopic disease [10]. In Indonesia, prevalence of psychosocial emotion disorder internalizing and attention aspects in allergic rhinitis children were 85,7% and 80% [11]. This study showed, in internalizing aspect, the prevalence was 1 (12.5%) and 3 (67.7%) patients whose got immunotherapy more 6 months-1 year and 2-3 years.

There are two mechanisms involved in triggering internalizing disorder in allergic rhinitis children. Those are behavioral changes and biologic mechanism. Behavioral changes caused by long term stress due to symptoms and therapy of chronic disease. Even the morbidity were low, but the low quality of life has been massively reported [10].

Potential biological mechanisms for this association between allergic diseases and internalizing disorders proposed include the release of interleukin-1β in hypersensitivity reactions,which activates the hypothalamic-pituitary-adrenal axis stimulating the release of cortisol and which modifies serotonin release leading to mood disturbances. However, mouse models have proposed a direct relationship between antigen exposure and altered brain function leading to increased anxiety. T helper 2 (Th2) cytokines production in the prefrontal cortex and olfactory bulbs of rats with tree pollen and Ovalbumin-induced allergic rhinitis has been demonstrated. These findings support the hypothesis that mediators of allergic inflammation may directly influence the centers of the brain involved in emotions and socialization [10].

Risk of psychosocial emotion disorder in school and pre-school aged children were 13% and 10% [5]. In this study, based on PSC-17 total score which represent risk of psychosocial emotion disorder, the prevalence only found in 1 (12.5%) patient whose got immunotherapy for 6 months – 1 year. Atopic disease and psychosocial has two way relationship, which atopic disease affect psychosocial more than the other way. Therefore, mental health of atopic disease patient needs special concern, in order to discontinue the relationship [12].

Allergic rhinitis children before treatment, have higher impulsivity and inattention rate [13]. Prevalence of ADHD are higher than general population, 1% vs 0.5% ($p < 0.001$) [8]. In Indonesia, prevalence of ADHD risk in allergic rhinitis children are 83.3%.[11] In this study, risk of ADHD consistently decrease, as the immunotherapy duration increase. Prevalence of ADHD risk are in 2 (67.7%), 3 (37.5%), 2 (20.0%), and 1 (11.1%) patients whose got immunotherapy 0-6 months, 6 months-1 year, 1-2 years, 2-3 years. Allergen exposure in allergic rhinitis children will induce neuroimmune inflammation, which clinically manifest as ADHD [14].

In this study, days of immunotherapy duration mean in allergic rhinitis patients with and without risk of ADHD are 461 vs 743 days. Immunotherapy duration are significantly related to risk of ADHD ($p = 0.049$), and has weak correlation ($r = 0.326$).

In allergic rhinitis, allergen exposure will be presented by APC to naïve T lymphocyte. Allergen bound dendritic cell interact with naïve T cell and induced polarization aim to Th2 response. Activated T cell migrate to bone marrow and produce inflammatory cell such as, basophil, eosinophil, and mast cell. The activation process involve (1) Newly activated TH lymphocyte by allergen, will have Th2 phenotype which release IL-3, IL-4, IL-5, IL-9, IL-13, eotaxin (CCL11), and GM-CSF; (2) Released of IL-4 or IL-13 will induce B cell differentiation into plasma cell which synthesize IgE. Next exposure of immunocompetent cells to the same allergen leads to mediator release and further activation of Th2 cell. IgE covered mast cell will bond to allergen, and release histamine, main mediator of allergy. Histamine is the most consistent stimulant in hyper-responsiveness, and also have H1, H2, and H3 receptor. H1 receptor found in T cell, B cell, monocyte, and lymphocyte. Stimulation of this receptor will induce inflammation of the respiratory, gastrointestinal tract, and skin. Signal of H1 receptor play a role in inducing proliferation process of T cell and B cell. It releases

cytokine and antibody through a pathway mediated by antigen receptor. H1 receptor have an extensive role in inflammatory process. H2 receptor play a role in itchy and painful sensation of the skin, permeability increase, and peripheral vasodilatation. H3 receptor increase neurotransmitter release [4].

Immune system and brain communication was important, because brain have a role in immune response (fever, sickness behavior, general behavior, and immunomodulation). It is mediated by several pro-inflammatory cytokine [15].

Cytokines have the ability to neuromodulate the brain during infection and inflammation. Its presence is also found in healthy brain, regulating the mechanism of homeostasis and behavior such as sleep, memory, and metabolism. Cytokine receptors are found in microglia, astrocytes, neurons, endothelial cells, and oligodendrocytes, which are distributed in the central nervous system (CNS) with different amounts, in different areas of the brain, of each individual. Cytokines are also produced in the brain in response to peripheral cytokine production, which indicates that cytokine formation signals are transmitted from the periphery to the brain.[16] The transmission occurs through several mechanisms [15].

- Cytokines in blood diffuse through blood-brain barrier which is permeable and adjacent to circumventricular organs. In this case, cytokines can interact directly with microglia and astrocytes.

- Interaction of cytokines and endothelial cells in the brain. Endothelial cells have IL-1 receptors and transmit cytokine signals to the brain

- Direct nerve activation by peripheral cytokines through the vagal nerve and catecholaminergic circuit of sympathetic nervous system

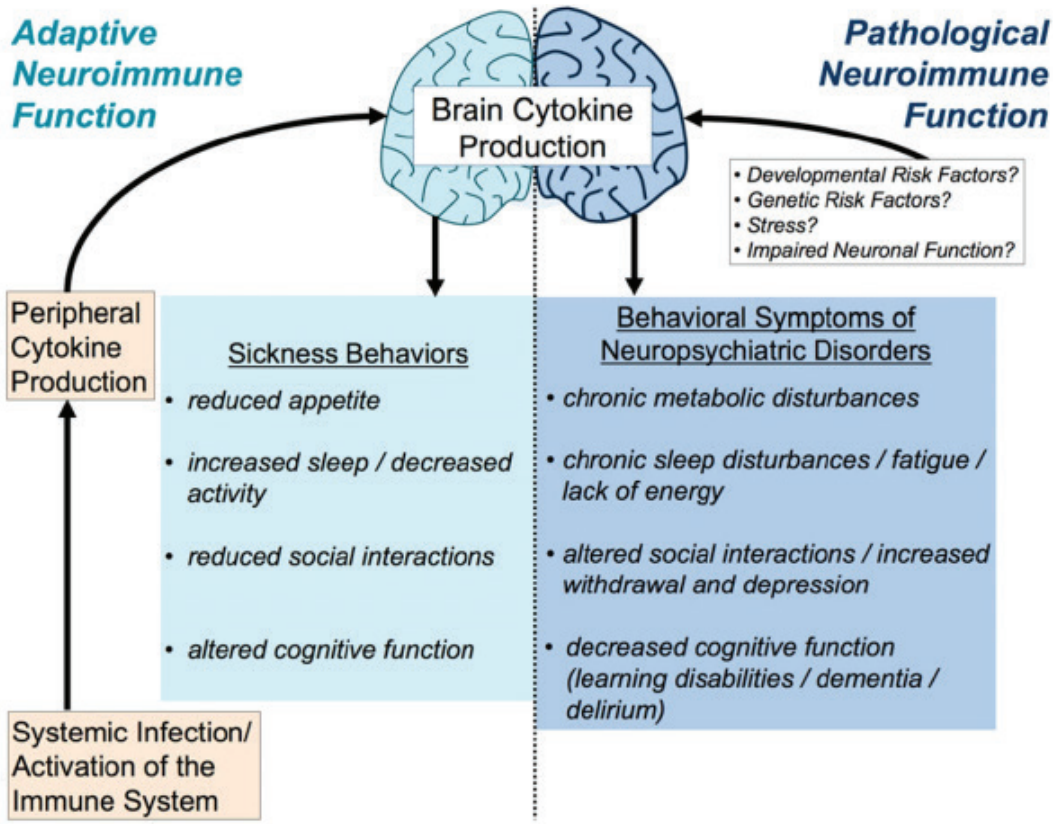

Figure 1 Adaptation function and neuroimmune pathology increase cytokine production and influence behavior.

Peripheral cytokine response induce brain cytokine production. Brain cytokine induce behavioral change including decrease social interaction and cognitive disorder.

Source: Bilbo SD, and Schwarz JM, 2012. The Immune System and Developmental Programming of Brain and Behavior. Front Neuroendocrinol, 33: 267-86.

Brain glia, consist of astrocytes (astroglia) and microglia, associated with behavioral disorders mediated by cytokines. Astrocytes are derivatives of nerve progenitors and have many functions, including neurotransmitter, maintaining the integrity of blood brain barrier, providing structural support, releasing neurotropic factors, and bind to synaptic transmission. Whereas microglia are derivatives of myeloid derivatives from bone marrow, which spread over the CNS, at least 15% of the CNS cell population. Initially myeloid cells migrate from bone marrow to brain parenchyma and terminally differentiate into microglia. Substitution of brain microglia is limited, in the absence of inflammatory stimulation microglia have a branched morphology, small sized cells with many arms and thin. In the resting phase, microglia actively monitor their microenvironment by emitting their projections. In the active phase, microglia appear unbranched, large and dense without arms. Activated microglia can have macrophages like function, such as scavenging, phagocytosis, antigen presentation, and produce inflammatory cytokines, so that they can affect neuron survival, proliferation, function, and synapses plasticity [15, 17].

Microglia and astrocytes work together in order to improve and regulate neuroinflammation response. Active glia will produce both inflammatory and anti-inflammatory cytokines. Inflammatory cytokines include IL-1β, IL-6, and TNFα which can induce and maintain behavioral disorders. The cytokine signal also triggers release of secondary inflammatory mediators such as prostaglandins and nitric oxide. Based on the glia response time, microglia are activated first and then astrocyte will increase the inflammatory signal. The neuroinflamation process usually occurs transiently, when the immune stimulus is finished, microglia will return in resting phase. However, the existence of a continuous neuroinflamation process will lead to maladaptation [15].

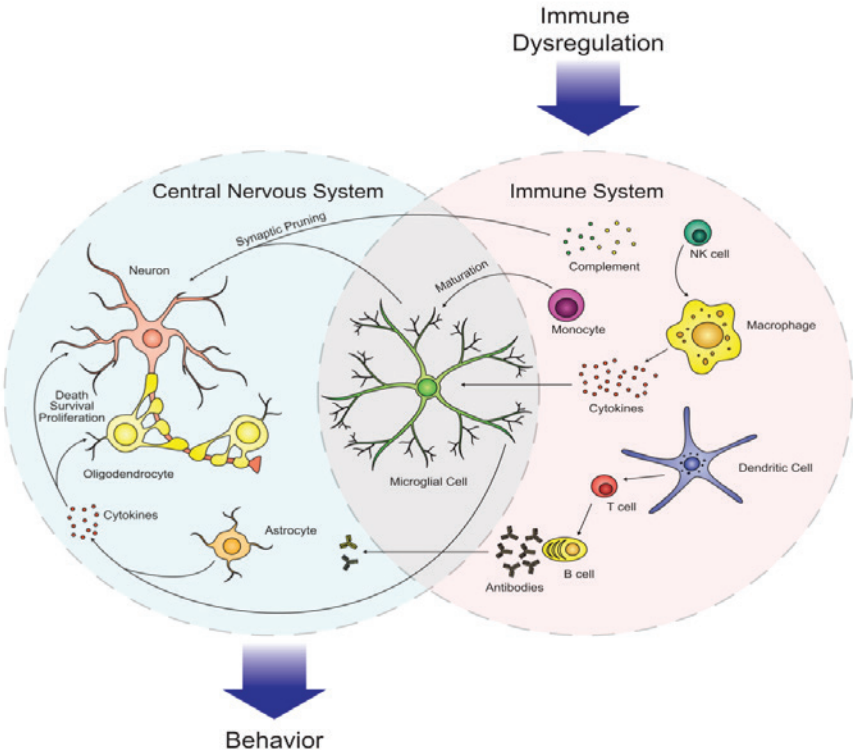

Figure 2. Immune dysregulation effect to behavior

Source: Onore C, Careaga M, and Ashwood P, 2012. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun, 26:383-92.

Immune dysfunction involves interaction of several types of cells, from natural and acquired immune systems. Several factors in immune system have an impact on CNS function. Increased cytokine production, such as TNFα and IL-1β, will inhibit neurogenesis and trigger cell death, whereas Il-6 can induce growth and proliferation of neurons and oligodendrocytes. Increased levels of complement protein can participate in synaptic scaling, opsonizing synapses and targeting for phagogocytosis by microglia. Activated microglia can also mediate synaptic pruning through MHC1 interactions. Therefore, it can be concluded that the presence of immune system dysfunction can cause behavioral disorders, such as cognitive function disorders, social environment withdrawal, and deviant behavior [17].

Relationship between allergic rhinitis and ADHD results from increased Th2 activity and secretion from the anti-inflammatory cytokines IL-4, IL-5, IL-9, IL-10, and IL-13. Th2 cytokines play an important role in induction process of the production of allergen-specific IgE (IL-4), and the entry of eosinophils into allergic inflammatory sites (IL-5). Inflammatory cytokines can activate neuroimmune mechanisms that involve brain circuits that affect behavior and emotions, and indirectly influence neuronal activity of brain structures through activation of hypothalamic-pituitary-adrenal pathway. In addition, inflammatory cytokines will also disrupt the metabolism of central neurotransmitters such as norepinephrine and dopamine which are known to play a role in the pathology of ADHD [18].

The mechanism of allergic rhinitis comorbidity with ADHD, is also thought to be due to stress exposure at an early age of child. Stress is related to the development of typical brain structure of ADHD, which affects cognitive function, and leads to onset of ADHD symptoms [18].

Sleep disorders are common finding in allergic rhinitis children. Minor sleep restriction cause specific circuits dysfunction in brain, especially prefrontal cortex, and negatively impact cognitive function and behavior. Impaired executive function is mostly found in children with ADHD. Therefore, sleep disorders are considered to have an important synergistic role in increasing risk of ADHD in allergic rhinitis children. In addition, allergic diseases and ADHD are thought to have similar genetic mechanisms. Signal transducers and activators of tranion 6 (STAT6) are involved in immune system regulation, cell proliferation, and apoptosis, which are thought to play a role in the pathogenesis of ADHD, and closely related to allergic diseases [18].

Immunotherapy has an allergen-blocking effect by IgG4 at the level of APC with the effect of preventing IgE production which facilitated by Th2 cells activation. In addition, immunotherapy immunologically worked by repressing eosinophilia, reducing immune reactivity, and shifting Th2 domination to Th1. Treg cells play a major role in immunotherapy. Treg cells are effective in regulating Th2 and Th1, where the clinical effect of immunotherapy is related to Th1 / Th2 balance. Increased production of allergen-specific IgG4 will block allergic inflammatory cascade (as a result of allergen and IgE bond in mast cells). Allergen-specific IgG4 has activity against IgE and is able to survive long term. So that specific immunotherapy also produces early effects and long-term persistent effects in reducing symptoms and treatment needs, as well as decreasing hyper-reactivity [4].

Improvement of ADHD symptoms in allergic rhinitis children is seen in the use of drugs that can regulate inflammation.[14] Administration of immunotherapy as a management of house dust mite allergy as a cause of allergic rhinitis is thought to be able to control allergic symptoms, so that the impact to risk of psychosocial emotion disorders and ADHD is low [3].

Main focus of allergy management is symptom reduction. Specific immunotherapy can reduce symptoms and treatment needs, and give long-term effects in preventing the development of further allergies. Specific immunotherapy is also useful as an anti-inflammatory, resolve causes, and prevent allergic airway diseases [4].

Limitations of this study, first the design used is cross sectional, so unable to detect increase or decrease trend of risk of psychosocial emotion disorders and risk of ADHD. Second, samples number inadequately represent allergic rhinitis children population. Third, immunotherapy duration is not long enough, so that the clinical effect might be not significant. Fourth, confounding factors not included in this study included

food allergies, exposure to environmental allergens, patient nutritional status, and allergic rhinitis severity.

Conculsion

The highest prevalence of the risk of psychosocial emotion disorder are in allergic rhinitis children whose got immunotherapy more than 3 years. Highest prevalence risk of ADHD were in allergic rhinitis children whose got immunotherapy more than 6 months. Immunotherapy duration weakly correlated with risk of ADHD.

Conflicts of Interest : None declared

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Ethical Clearance : Approved by the Ethics Commission for Biomedical Research on Humans, Dr. Soetomo General Hospital, Surabaya. Ethical number published on June 13th 2017, 404/Panke.KKE/VI/2017.

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