

Role of Histamin 1 Receptor as Risk Factor for Hypertrophic Concha Caused by Allergic Rhinitis Immunohistochemically

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Abstract: Background: Allergic rhinitis and non allergic rhinitis can caused hypertrophic concha especially in inferior turbinate. Main complain of hypertrophic concha is nasal obstruction which caused to decrease of quality of live. Until now, there has not been any study about role of histamine 1 receptor as risk factor hypertrophic concha caused of allergic rhinitis by immunohistochemistry. **Methods:** This research was analytical observational by case control study on the sample which include inclusion criteria. Histamine 1 receptor be examined by immunohistochemistry with negative and positive value. **Result:** From this research, there is correlation between postive value at H1 receptor with hypertrophic concha caused by allergic rhinitis, which $p:0,001$; OR:30 and 95% CI = 5,833-154,29. It mean is H1 receptor with positive value at allergic rhinitis have more than H1 receptor with negative value. **Keywords:** Histamine 1 receptor, Hypertrophic concha, Allergic Rhinitis, Immunohistochemistry.

Background:

Although hypertrophic concha is not life threatening disease but this condition often disturb quality of life and become financial burden for the patients.¹ It's often found in allergic rhinitis and non allergic rhinitis patients, which most symptom is nasal obstruction.² Prevalence rate is high. In US and Europe, the prevalence rate of hypertrophic concha about 10-25%.³ Hypertrophic concha pathogenesis is resulted the change of airway connective tissue, called airway remodelling. Both caused allergic rhinitis and non allergic rhinitis.⁴

Histamine is mediator which main role in allergic rhinitis and non allergic rhinitis and influence the other mediator.⁵ Role of histamine is especially in rapid phase allergic rhinitis. Histamine 1 receptor expression found in vascular endothelial can increase vascular permeability and may cause swelling of tissue and nasal airway resistance. Exposure of chronic allergic inflammation can caused to change structure of tissue including thickening epithelium, hypertrophic of goblet cell and neovascularitation.⁶ However, research on the role of histamine as angiogenic risk and etiologic risk of hypertrophic concha in allergic rhinitis, has never been conducted.

Sample and Methods

This research is analytic observations study by case control design. Samples criteria included hypertrophic concha ensured by anamnesis found permanent nasal obstruction, physical examination found enlargement of inferior turbinate had exceeded partial nasal cavity (B classification from Yanez),

rhinomanometry examination by Rhynometri Gama IV equipment with ratio of expiration pressure more than 1,33 mmHg and histopathologic examination found thickening of basal membrane, enlargement of goblet cell, cystic degeneration of gland, increased count of eosinophilic cell and swelling of stroma in case and control group.

Hypertrophic concha caused by allergic rhinitis with criteria of moderate to severe degree persistent (WHO ARIA 2008 criteria), during anamnesis, it was found that allergic for house dust mite with conformed by skin prick test, used Alystic prick Hypens Pharma production, specific IgE examination for house dust mite by chemiluminescent immunoassay technic which used Immulite 2000 systems (Siemen, USA) and histopathologic examination on case group. Hypertrophic concha patient caused by non allergic rhinitis, at anamnesis not found allergic for house dust mite which conform by skin prick test, specific IgE for house dust mite, and histopathology examination for control group. Exclusion criteria at this research is patients using nasal decongestion drug. Patients by rhinomanometry found diferent value more than 0,05 mmHg after taking decongestive nasal drops. Pregnant woman and hypertrophic concha tissue broke so it can't be examined.

Histamine 1 receptor examined by immunohistochemistry using Histamine1 receptor primary antibody (RbpAb, ab 140815, Abcam, Hampshire, UK). It was examined by anatomic pathologies from Medical Faculty Sumatera Utara University and Indonesia University, using image J software. Immunohistochemistry result consist of 0,+1,+2 and +3. This value converted became negative (-) value if 0 and +1 score and positive(+) value if +2 and +3 score.

Result

This research found 58 hypertrophic concha patients consist of hypertrophic concha; 29 caused by allergic rhinitis and 29 caused by non allergic rhinitis.

Characteristic of hypertrophic concha based on etiologi at table 1 and 2.

Table 1 Hypertrophic concha based on sex

	Allergic Rhinitis		Non Allergic Rhinitis	
	n	%	n	%
Men	4	13,8	3	10,3
Woman	25	86,2	26	89,7
Totally	29	100	29	100

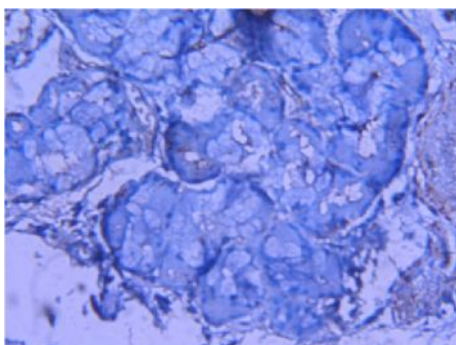
At this table, both hypertrophic concha caused allergic rhinitis nor non allergic rhinitis more woman than men.

Tabel 2 Hypertrophic concha based on age group

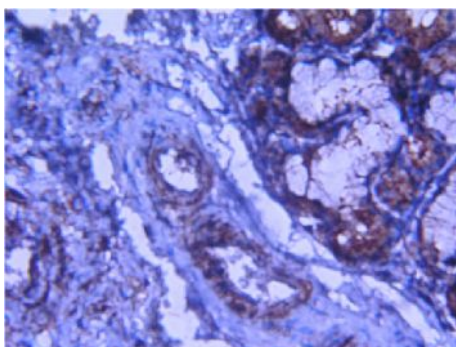
	Allergic Rhinitis		Non Allergic Rhinitis	
	n	%	n	%
15 - 24	25	86,2	19	65,5
25 - 34	3	10,3	8	27,5
> 35	1	3,5	2	7,0
Totally	29	100	29	100

Based on age group, the most age group were 15-24 years old, both in hypertrophic concha caused allergic rhinitis nor non allergic rhinitis.

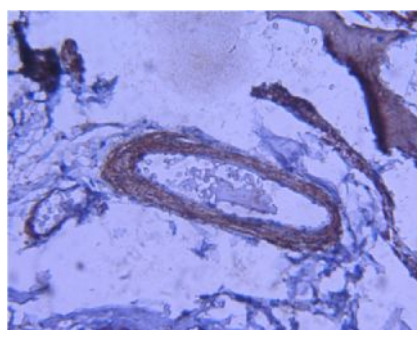
The result immunohistochemistry examination



Sample No. 121940 IHC H1Receptor, NAR +1



Sample No. 13027 IHC H1 Receptor RA +2



Sample No. 121498 IHC H1 Receptor, RA +3

Inferensial Analysis

Table 3 Immunohistochemistry result of Histamine 1 receptor in hypertrophic concha

	Hypertrophic Concha				OR	p value	95% CI	
	Allergic Rhinitis		Non Allergic Rhinitis					
	n	%	n	%				
H1 receptor (+)	27	75,0	9	25,0	30	0,0001/<0,0001	5,833	154,29
H1 receptor (-)	2	9,1	20	90,9				
Totally	29		29					

At the 3rd table, significant correlation can be seen between positive H1 receptor with hypertrophic concha caused by allergic rhinitis which p value = 0,001, OddsRatio = 30 and 95% CI = 5,833-154,29. it means that positive H1 receptor in hypertrophic concha caused by allergic rhinitis is 30 times more likely to cause hypertrophic concha than the negative H1 receptor.

Discussion

This research has been conducted since September 2012 to January 2014, and managed to collect up to 73 patients. Fifteen (15) patients were excluded because ten (10) patients, from the result of skin prick test examination and specific IgE for house dust mite presented hypertrophic concha caused by allergic rhinitis but histopathological examination did not suggest signs of allergic rhinitis. In addition, skin prick test examination and specific IgE for house dust mite found non allergic rhinitis but histopathological examination found allergic rhinitis signs. Five samples, however, broke. So leaving only 58 patients as sample of this study, which consist of 29 patients with hypertrophic concha caused by allergic rhinitis and 29 patients with hypertrophic concha caused by non allergic rhinitis.

Analysis result on data from this research presented Histamine 1 receptor expression contribute as risk factor hypertrophic concha caused by allergic rhinitis. Significant differentiation can be seen between positive histamin 1 receptor with negative histamine 1 receptor, with the value of p value: 0,001 ($p < 0,05$); OR:30 and 95% CI:5,833-154,29. Histamine 1 receptor is most important mediator in allergic process, induced by activated link of phospholipase C-generation inositol 1,4,5-triphosphate (Ins(1,4,5)P3) dan 1,2-diacyl Glycerol which can increase Ca^{2+} intraseluler.⁶ Histamine can caused vasodilatation and increased vascular permeability and caused leaking at wall of vascular or endothelial lining. It can cause extravasation of plasma, so presented oedem and swelling in sinusoid. Histamine caused an increase in vasculary permeability because signaling effect histamine 1 receptor which contactation of F-actin fibrille on endothelial sikloskeleton so that formed gap in venule post capillary and formed macromolecul extravasation. Chronic allergic inflamation exposure caused thickening epithelial, smooth muscle hypertrophic, goblet cell hyperplasia, fibrotic sub epithelial, plasma cel infiltration and change of vascularr structur formed neovascularitation which called airway remodeling. Change of nasal airway tissue especially found in nasal superficial and submucosal lining caused inferior turbinate became hypertrophic.^{7,8,9,10,11}

In hypertrophic concha caused by non allergic rhinitis, histamin did not contribute. Pathogenesis of hypertrophic concha caused by non allergic rhinitis suspect to resulted nasal hyperreactivity to non specific exposure which corellated with neurogenic inflamation mechanism with precipitatus factor which corellated with weather and irritation factor.^{12,13,14,15,16} Non specific exposure caused neurogenic inflamation so that formed end nerve and airway epithelial damage. Sensory nerve fiber stimulated at both afferent nor efferent sensory end nerve, and then sensory nerve fiber produced neuropheptide such as P substance, *calcitonin gene-related peptide* (CGRP), and A neurokinin contained in nerve fiber and parasimphatetic end nerve. This neuropheptide caused smooth muscle contraction, secretion of goblet cell mucous, plasma exudation from capillary so that formed change of nasal airway structur.¹⁶ Immunohistochemistry examination showed intensity of immunoreaktivitas of histamine 1 receptor clearer in hypertrophic concha caused by allergic depent of caused by non allergic.¹⁷ Nakaya, Takeuchi, Kondo (2004), in their research reported location of histamine 1 receptor subtype in nasal turbinate of allergic rhinitis patients by immunohistochemistry examination found at arteriole is 3+, vein and venule is 3+, cavernous sinus is 3+, nerve is 3+ whereas at epithelial is 2+ and at glan only 1+. However, diferent from this research, which was conducted do at hypertrophic concha caused by allergic rhinitis and non allergic rhinitis. This research, however, inidentical in histophatological between nasal turbinate in allergic rhinitis with hypertrophic concha caused by allergic rhinitis.

This research found that histamine 1 receptor conrtributed as risk factor to cause hypertrophic concha caused by allergic rhinitis, then it become consideration in management of allergic rhinitis to protect form hypertrophic concha by H1 antihistamin long time administration. Some antihistamins such as cerebastine, are active metabolite from ebastine (selective antagonist histamine of H1 receptor second generation) reported to have angiogenic potential by invitro research using Human Umbilical Vein Endothelial Cell and Human Pulmonary Artery Endothelial Cell and by invivo at Human Umbilical Vein Endothelial Cell assay.^{19,20} The research from Le (2013) reported histamine sinergictical on VEGF production can decrease with diphenhydramine (H1 receptor antagonist) administration but could not with cimetidine (H2 receptor antagonist).²¹

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