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ROLE OF HISTAMINE 1 RECEPTOR AS RISK FACTOR HYPERTROPHIC CONCHA CAUSED OF ALLERGIC RHINITIS BY IMMUNOHISTOCHEMISTRY 1Indra Zachreini, 2Suprihati, 3Muhammad Nadjib Dahlan Lubis, and 4Adi Koesoema Aman 1ENT-HNS Departement Malikussaleh University, Lhokseumawe, Aceh, Indonesia, dr_indrazachreini@yahoo.com 2ENT-HNS Departement Diponegoro University, Semarang, Jawa Tengah, Indonesia, suprihatiw@yahoo.com 3Anatomi Phatologic Departement Sumatera Utara University, Medan, Indonesia, mnadjiblubis@gmail.com 4Clinic Phatologic Sumatera Utara University, Medan Indonesia, adikoesoemaaman@yahoo.com **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 is not 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 at the sample which included of inclusion criteria.

Histamine 1 receptor be examined by immunohistochemistry which its values involved as negative and positive. Result: 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 hypertropic 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 was found in vascular endothelial can increase vascular permeability caused swelling of tissue and nasal airway resistance. Exposure of chronic allergic inflammation can caused to change structure of tissue include thickening epithelium, hypertrophic of goblet cell and neovascularitation.

6 However, how do role of histamine as angiogenic risk and etiologic risk of hypertrophic concha in allergic rhinitis, never researched. Sample and Methods This research is analitic observations study by case control design. Samples were include inclusion criteria such as hypertrophic concha which ensured by anamnesis found permanent nasal obstruction, physical examination found enlargement of inferior turbinate had eceeded partially of nasal cavity (B classification from Yanez), rhinomanometry examination by Rhynometri Gama IV equiptment which ratio of expiration pressure more than 1,33 mmHg and histopathologic examination were 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 were caused allergic rhinitis with criteria of moderate to severe degree persistent (WHO ARIA 2008 criteria), which in anamnesis found 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 chemilunescent immunoassay technic which used Immulite 2000 systems (Siemen, USA) and histopathologic examination on case group.

Hypertrophic concha patient caused non allergic rhiniis, at ananmnesis 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 drops nasal decongestive.

Pregnant woman and hypertrophic concha tissue broke so it can to examination.

Histamine 1 receptor examined by immunohistochemistry used Histamine1 receptor primary antibody (RbpAb, ab 140815, Abcam, Hampshire, UK). It examined by anatomic pathologies from Medical Faculty Sumatera Utara University and Indonesia University, which used 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 hypertrophic concha amount 58 patients consist of hypertrophic concha caused allergic rhinitis amount 29 patients and non allergic rhinitis amount 29 patients. 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 than woman depent 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 Inferensial Analysis Table 3

Immunohistochemistry result	of Histamine 1 receptor	n	%
H1 receptor (+)		27	75,0
H1 receptor (-)		2	9,1
Totally		29	100

At the 3rd table, shown presented significant correlation between positive H1 receptor with hypertrophic concha caused by allergic rhinitis which p value = 0,001, Odds Rasio = 30 and 95% CI = 5,833-154,29.

it mean was positive H1 receptor in hypertrophic concha caused by allergic rhinitis had chance more than 30 times to cause hipertrophic concha depent with negative H1 receptor. Discussion This research did since September 2012 to January 2014, which collected amount 73 patients. Fifteen patients exluded because ten patients, the result of skin prick test examination and specific IgE for house dust mite presented hypertrophic concha caused by allergic rhinitis but histopathological examination not suggest signs of allergic rhinitis.

And otherwise skin prick test examination and specific IgE for house dust mite found non allergic rhinitis but histopathological examination found allergic rhinitis signs. Five persons, their samples were broke. So that amount of samples which we can do statical

analysis in this research only 58 patients. consist of 29 pateints 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 where it were significant differently between positive histamin 1 receptor with negative histamine 1 receptor, the value was 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 phospoliphase 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 so that leak at wall of vascular or endothelial lining. It can caused extravasation of plasma, so presented oedem and swelling in sinusoid. Histamine caused increase vascular permeability because signaling efect histamine 1 receptor which contraction of F-actin fibrille on endothelial sikloskeleton so that formed gap junction 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 vascular 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, different from this research, which do at hypertrophic concha caused by allergic rhinitis and non allergic rhinitis. There were differentiated histopathological between nasal turbinate in allergic rhinitis with hypertrophic concha caused by allergic rhinitis. Base on this research found that histamine 1 receptor contribute as risk factor to caused 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.

Several of antihistamin such as cerebastine, constitute active metabolite from ebastine (selective antagonist histamine of H1 receptor second generation) reported had 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 sinergistical on VEGF production can decreased with diphenhydramine (H1 receptor antagonist) administration but did not with cimetidine (H2 receptor antagonist).²¹ References 1. Maria PF., Cesare PG., Damiani V., Bellusi I., 2003.

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