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The expression of 11 β–hydroxysteroid dehydrogenase in severe allergic rhinitis

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ABSTRACT:

Objective: To clarify the roles of 11 β-HSD in resistance to glucocorticoid therapy for allergic rhinitis, a case series study was conducted.

Methods: The patient group consisted of 20 subjects with allergic rhinitis, aged from 21 to 46 years (mean age 26.5), who showed persistent GC resistance necessitating surgical removal of the inferior turbinate after 6 months of GC treatment. The patients with poor response to GC treatment for 6 months were defined as GC-resistant. The control group consisted of 10 subjects aged from 16 to 39 years (mean age 24.5) who underwent maxillofacial surgery, from whom nasal tissues were taken and who did not receive GC treatment. Nasal mucosal tissues from patients and control subjects were examined immunohistochemically. The sections were washed with 0.01 M phosphate-buffered saline (PBS; pH 7.2) containing 0.15 M NaCl and 0.01% Triton X-100, and incubated for 2 h with rabbit polyclonal anti-11 β–HSD1 and 11 β–HSD2 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), each diluted 1:200 in PBS containing 0.1% bovine serum albumin. Immunostained sections were assessed under an Olympus microscope with an eyepiece reticule at 200× magnification. Cell counts are expressed as means per high-power field (0.202 mm^2). Control group means (arithmetic mean ± SD) were compared with patient group means by Mann–Whitney U-test at P = 0.05.

Results: Although 11 β–HSD1 was expressed to a similar extent in patients and controls, 11 β–HSD2 was expressed more significantly in patients with severe allergic rhinitis, resulting in an increased HSD-1/HSD-2 ratio. The significantly increased expression of 11 β–HSD2 in the nasal epithelium and submucosal inflammatory cells of patients with severe nasal allergy was observed in the present study.

Conclusion: Our findings suggest that 11 β-HSD2 plays an important role in resistance to glucocorticoid therapy for allergic rhinitis, and its expression might be used as an additional parameter indicating steroid resistance in allergic rhinitis.

KEYWORDS: allergic rhinitis, 11 β-hydroxysetroid dehydrogenase, glucocorticoid resistance, glucocorticoid therapy, glucocorticoid response

INTRODUCTION

Glucocorticoids (GCs) are commonly used as anti-inflammatory agents in the treatment of chronic allergic diseases, including allergic rhinitis. However, these clinical benefits are sometimes limited because some patients demonstrate persistent tissue inflammation despite repeated and high doses of GC treatment. Studies of GC receptors (GR), NF-κB and other mediators in underlying mechanism of GC resistance have been reported (1,2). The 11β-hydroxysteroid dehydrogenase (11β-HSD) is a tissue-specific regulator of glucocorticoid responses, inducing the interconversion of inactive and active glucocorticoids. The 11β-HSD has two isoforms, 11β-HSD1, which converts inactive 11-keto corticosteroids into active 11-hydroxy corticosteroids, thereby potentiating the effects of endogenous glucocorticoids, and 11β-HSD2,which acts as a classic dehydrogenase by converting active 11-hydroxylated cortisol and corticosterone into inactive 11-keto forms of cortisone and 11-dehydrocorticosterone, respectively (3). Here, to clarify the roles of 11 β-HSD in resistance to glucocorticoid therapy for allergic rhinitis, a case series study was conducted.

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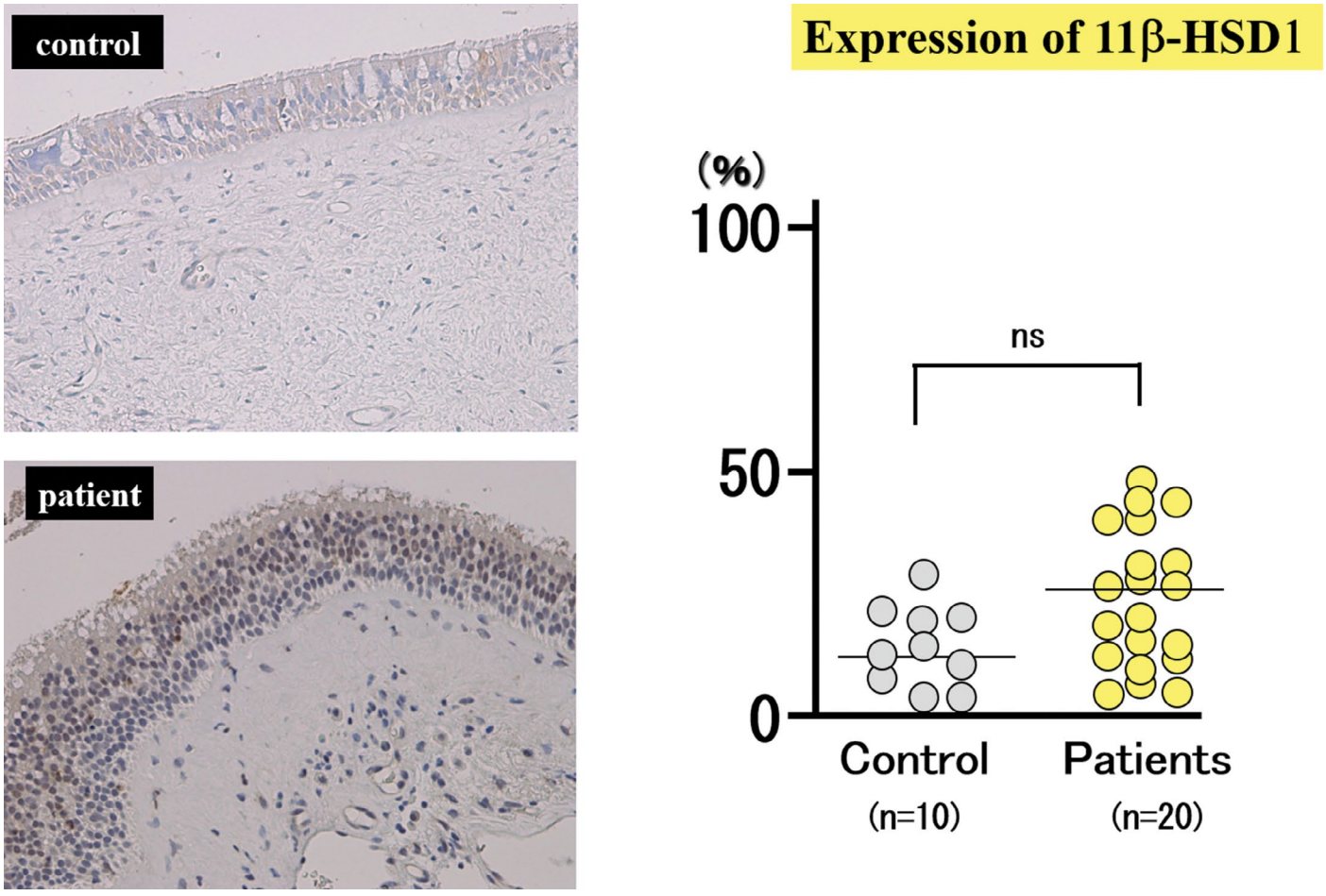

Fig. 1. Representative pathological findings of 11β-HSD1 immunoreactivities in the nasal mucosa of patients with severe nasal allergy and controls. (original magnification ×100).

SUBJECTS AND METHODS

All patients were treated by experienced ENT doctors at Yamagata City Hospital Saiseikan, Yamagata University Faculty of Medicine, and Tohoku Medical and Pharmaceutical University between February 2010 and August 2017. Informed consent was obtained under protocols approved by the Institutional Review Board. The patient group consisted of 20 subjects with allergic rhinitis, aged from 21 to 46 years (mean age 26.5), who showed persistent GC resistance necessitating surgical removal of the inferior turbinate after 6 months of GC treatment. The patients with poor response to GC treatment for 6 months were defined as GC-resistant.

The control group consisted of 10 subjects aged from 16 to 39 years (mean age 24.5) who underwent maxillofacial surgery, from whom nasal tissues were taken and who did not receive GC treatment. Nasal mucosal tissues were fixed in 10% formalin for 1 to 2 days, dehydrated through an ethanol series, and embedded in paraffin wax. Sections 3 μm thick were dewaxed in xylene and dehydrated. The sections were washed with 0.01 M phosphate-buffered saline (PBS; pH 7.2) containing 0.15 M NaCl and 0.01% Triton X-100, and incubated for 2 h with rabbit polyclonal anti-11 β–HSD1 and 11 β–HSD2 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), each diluted 1:200 in PBS containing 0.1% bovine serum albumin. Controls for nonspecific staining were incubated with 10 μg/mL mouse IgG1 (DAKO, Glostrup, Denmark). Sections were washed and incubated with biotinylated rabbit antibody to mouse IgG, IgA, and IgM (Immunotech, Tokyo, Japan) for 1 h.

The sections were incubated with Vectastain reagent (ABC Elite; Vector Laboratories, Burlingame, CA, USA), followed by 3.3-diaminobenzidine (Dojin Chemicals, Kumamoto, Japan) as the chromogen. Finally, the slides were counterstained with hematoxylin. Immunostained sections were assessed under an Olympus microscope with an eyepiece reticule at 200× magnification. Cell counts are expressed as means per high-power field (0.202 mm2). At least 2 sections were immunostained, and more than 5 areas were evaluated via the graticule. Results are expressed as positive cell ratio per field. Control group means (arithmetic mean ± SD) were compared with patient group means by Mann–Whitney U-test at $P = 0.05$.

RESULTS

Although 11 β–HSD1 was expressed to a similar extent in patients and controls, 11 β–HSD2 was expressed more significantly in patients with severe allergic rhinitis, resulting in an increased HSD-1/HSD-2 ratio. The significantly increased expression of 11β–HSD2 in the nasal epithelium and submucosal inflammatory cells of patients with severe nasal allergy was observed in the present study (Figure 1 and Figure 2).

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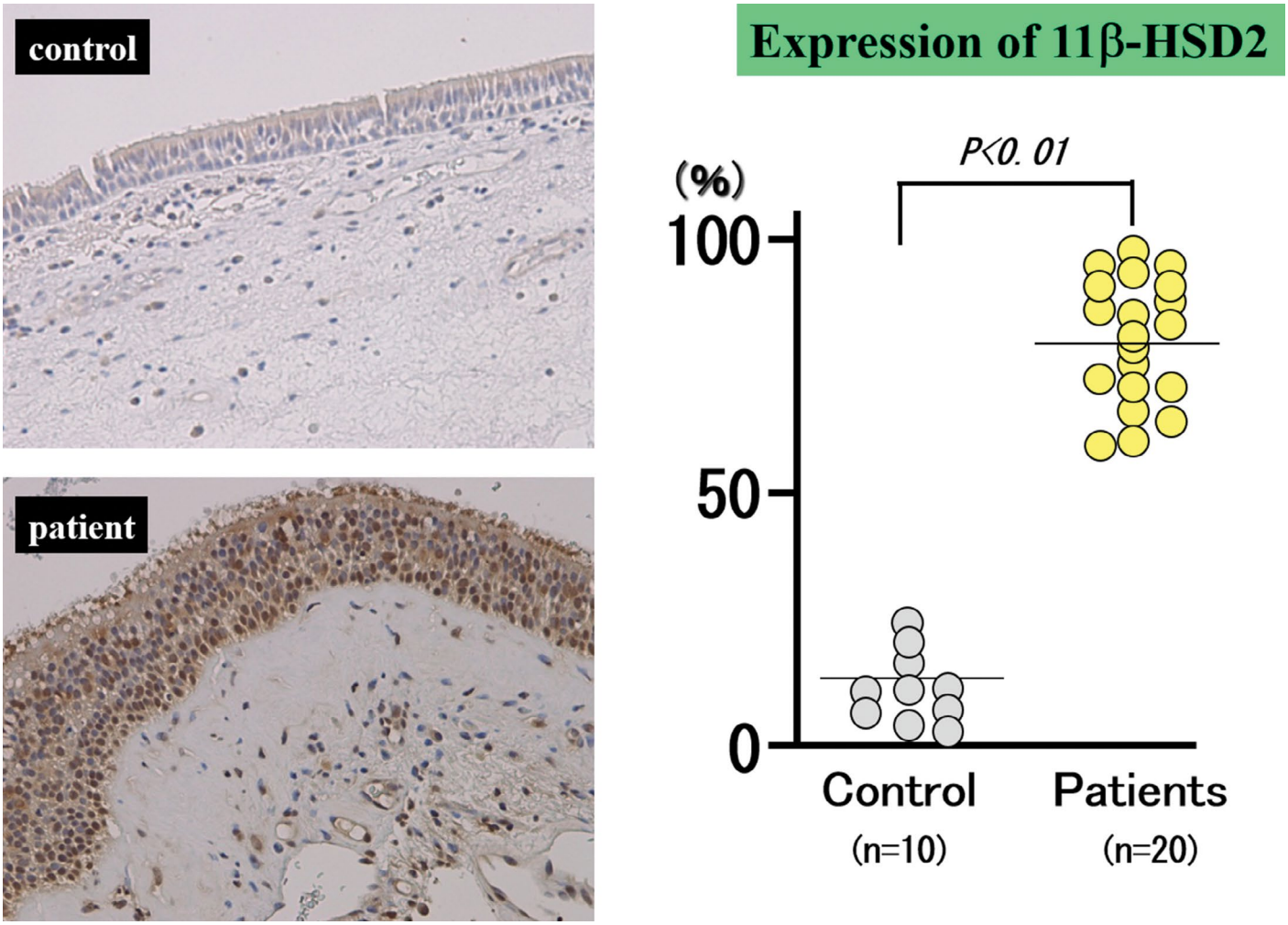

Fig. 2. Representative pathological findings of 11β-HSD2 immunoreactivities in the nasal mucosa of patients with severe nasal allergy and controls. (original magnification ×100).

DISCUSSION

The tissue levels of bioactive GCs are modulated by 11β-HSD which interconverts corticosteroids between inactive and active states; only the active forms of corticosteroids are able to interact with GR (3). Previous studies demonstrated that the expression of 11β-HSD1 was up-regulated and 11β-HSD2 was decreased in allergic rhinitis and chronic rhinosinusitis (3, 4). On the other hand, a recent report suggests that 11β-HSD1 and 11β-HSD2 are associated with steroid sensitivity in childhood nephrotic syndrome, acute lymphoblastic leukemia and 11β-HSD2 may contribute to steroid resistance (5). The 11β-HSD2 is also expressed in glucocorticoid-resistant leukemic cell lines where it contributes to prednisolone resistance (6).

The expression of 11β-HSD was regulated by Th2 type cytokines, chemical mediators and reagents (7,8). Taken together, our results strongly suggest that 11β-HSD2 expression in nasal mucosal epithelium and inflammatory cells could influence a patient's sensitivity to GC, and explain why some patients exhibit persistent GC resistance despite high doses and repeated treatment. The mechanisms underlying the development of steroid resistance remain unclear, and there are currently no reliable biomarkers to identify patients who will go on to develop steroid dependence and resistance.

CONCLUSION

Our findings suggest that 11β-HSD2 plays an important role in resistance to glucocorticoid therapy for allergic rhinitis, and its expression might be used as an additional parameter indicating steroid resistance in allergic rhinitis.

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