

Involvement of chronic epipharyngitis in autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)

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Abstract The epipharynx is an immunologically active site even under normal conditions, and enhanced immunologic activation is prone to occur in response to an upper respiratory infection, air pollution, and possibly to vaccine adjuvants. Due to the potential link between the central nervous system and immune function, a relationship between epipharyngitis and autonomic nervous disturbance as well as autoimmune disease has been suggested. Various functional somatic symptoms have been described after human papillomavirus (HPV) vaccination, although a causal relationship has not been established. We examined the epipharynx in young women showing functional somatic symptoms following HPV vaccination. Surprisingly, despite having minimal symptoms involving the pharynx, all patients were found to have severe epipharyngitis. In addition, significant improvement in symptoms was seen in most patients who underwent epipharyngeal treatment. Thus, we speculate that the chronic epipharyngitis potentially caused by the vaccine adjuvant may be involved in the pathogenesis of functional somatic syndrome (FSS) post-HPV vaccination. Further, we suggest that epipharyngeal treatment may be effective for various types of FSS regardless of the initial cause, as well as for some autoimmune diseases, and that this may be an important direction in future research.

Keywords Chronic epipharyngitis · Functional somatic syndrome · Human papillomavirus vaccine · Adjuvant

Abbreviations

HPV	Human papillomavirus
FSS	Functional somatic syndrome
HPA	Hypothalamic–pituitary–adrenal
ASIA	Autoimmune/inflammatory syndrome induced by adjuvant

Introduction

The epipharynx is rich in activated lymphocytes and is the most vulnerable site in the body in terms of upper respiratory infections and the effects of air pollution, including smoking. Although chronic epipharyngitis is not well-understood medical concept, the relationship between chronic epipharyngitis and number of diseases, including immune-mediated conditions such as arthritis, glomerular nephritis, and collagen disease, and various symptoms related to autonomic nervous disorders was proposed as early as 50 years ago [1]. Unfortunately, given the immature understanding of immunology at that time, an underlying mechanism could not be elucidated. Thereafter, the concept of chronic epipharyngitis became lost in medicine.

Human papillomavirus (HPV) vaccination is performed worldwide for prevention of cervical cancer [2, 3]. However, in a small number of cases, severe chronic fatigue syndrome/fibromyalgia-like symptoms have been reported following HPV vaccination and, despite the lack of a

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proven causal relationship, this potential adverse effect is of growing concern in Japan and elsewhere [4–8].

In this paper, we focus on the immunologic features of the epipharynx and discuss the possibility of chronic epipharyngitis as a trigger for immunologic disorders, as well as autonomic nervous system disorders with special attention paid to its possible causal relationship with adjuvant-induced functional somatic syndrome (FSS).

Chronic epipharyngitis and general diseases

Immunologic characteristics of the epipharynx

The surface of the epipharynx is lined with ciliated columnar epithelial cells, and secreted immunoglobulin A covers the surface of the epipharyngeal epithelium. There is an abundance of lymphocytes in the submucosal area, with a large number of lymphocytes colocalizing with epipharyngeal epithelial cells (Fig. 1). Importantly, epipharyngeal epithelial cells express major histocompatibility complex class II antigen, indicating their role in antigen presentation [9].

Phenotypic analysis of epipharyngeal lymphocytes identified the following:

- there are more B-lymphocytes than T-lymphocytes, and natural killer cells are a very minor cell population compared with the subset in peripheral blood
- helper T-lymphocytes (CD4 + cells) dominate cytotoxic T-lymphocytes (CD8 + cells), resulting in a high CD4 + cell/CD8 + cell ratio
- both T-lymphocytes and B-lymphocytes are highly activated, even in normal individuals

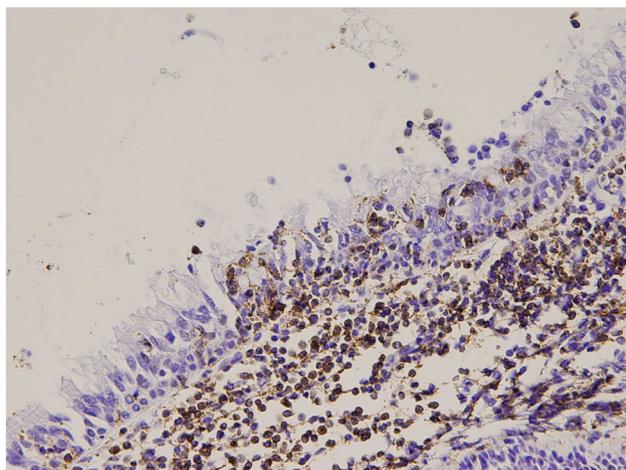


Fig. 1 Epipharyngeal surface of chronic epipharyngitis. Many lymphocytes locate within ciliated epithelial cells (anti-CD3 antibody, $\times 100$)

- the aforementioned characteristics of epipharyngeal lymphocytes are very similar to those of palatine tonsil lymphocytes
- activation of epipharyngeal helper T-lymphocytes is induced, whereas activation of B-lymphocytes is suppressed at the beginning of acute pharyngitis; however, marked activation of B-lymphocytes occurs during the recovery phase [9].

Definition of chronic epipharyngitis

The concept of chronic epipharyngitis was originally proposed by Horiguchi in the 1960s [1]. Through extensive studies, Horiguchi et al. demonstrated the following important findings, which may still be applicable in the present day and help us to understand the phenomena observed in patients with chronic epipharyngitis:

- chronic epipharyngitis is present in a significant proportion of the population
- although it may cause significant symptoms, epipharyngitis is rarely observed on routine otolaryngologic observation
- diagnosis of inflammation can only be made by direct surface abrasion of the epipharyngeal mucous membrane; in addition to cytological examination of smears obtained from the epipharyngeal mucosa, pain during and after abrasion of the epipharyngeal mucosa with local hemorrhage confirms the presence of epipharyngitis; abrasion pain and post-abrasive hemorrhage parallel the severity of inflammation found in the smears
- to treat epipharyngitis, a $ZnCl_2$ solution should be applied thoroughly to the epipharyngeal wall with a cotton applicator; the severity of abrasion pain and post-abrasion hemorrhage gradually reduces in response to treatment with $ZnCl_2$, suggesting resolution of the underlying inflammation.

As suggested by Horiguchi [1], it is still rather difficult to diagnose chronic epipharyngitis, even by standard endoscopic examination. However, the development of endoscopic technology has enabled physicians to detect anomalies of the epipharynx more precisely, which helps to diagnose chronic epipharyngitis.

Endoscopic findings of chronic epipharyngitis

In contrast with acute epipharyngitis, in which redness and discharge on the epipharyngeal surface are often observed, visible changes are unremarkable in chronic epipharyngitis as seen on standard transnasal endoscopic examination. In fact, as previously mentioned, Horiguchi concluded that the abnormality was rarely encountered on routine

otolaryngologic observation using posterior rhinoscopy 50 years ago [1].

At this time, Horiguchi also suggested that local hemorrhage during and after abrasion of the epipharyngeal mucosa is the hallmark of chronic epipharyngitis, and this phenomenon is ascribed to submucosal congestion. Fortunately, as a result of advances in image-enhanced endoscopic technology, band-limited light [10] has enabled physicians to discriminate chronic epipharyngitis by enhancing the congestion state with the abnormal appearance of the vasculature on the surface of the epipharynx (Fig. 2a, b). In addition, the epipharyngeal membrane in such cases is prone to bleeding in response to abrasion with a transnasal cotton swab (Fig. 2c, d).

Chronic epipharyngitis and related diseases

The epipharynx has high levels of immunologic activation, and because of its anatomic location, chronic inflammation in the epipharynx can have systemic effects via autoimmunity and the autonomic nervous system.

Chronic epipharyngitis-related symptoms and diseases

The various symptoms related to chronic epipharyngitis can be divided into three categories. The first category

includes the direct or radiated symptoms caused by epipharyngitis. Headache, shoulder stiffness, neck stiffness, sore throat, throat discomfort including globus sensation, tinnitus, post-nasal drip, persistent cough, and low-grade fever are included in this category [1]. These symptoms may present alone or in combination, even in individuals who have not been aware of any pharyngeal symptoms.

The second category is symptoms that arise because of dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis and alterations in the limbic system. Symptoms associated with dysfunction of the autonomic nervous system, such as orthostatic dysregulation, dizziness, gastrointestinal symptoms, general fatigue, and generalized pain, are included in this category [1].

The third category is an associated immune-mediated mechanism caused by focal inflammation of the epipharynx. Glomerulonephritis, such as immunoglobulin A nephropathy [11], dermatitis, such as chronic urticaria [12] and pustulosis palmoplantaris, arthritis, such as reactive arthritis and sternocostoclavicular hyperostosis, and some other autoimmune diseases are possibly related to chronic epipharyngitis [1].

Given that the epipharynx is vulnerable to the effects of smoking and air pollution, chronic inflammation of the epipharynx is likely to be accelerated in smokers. In fact, in

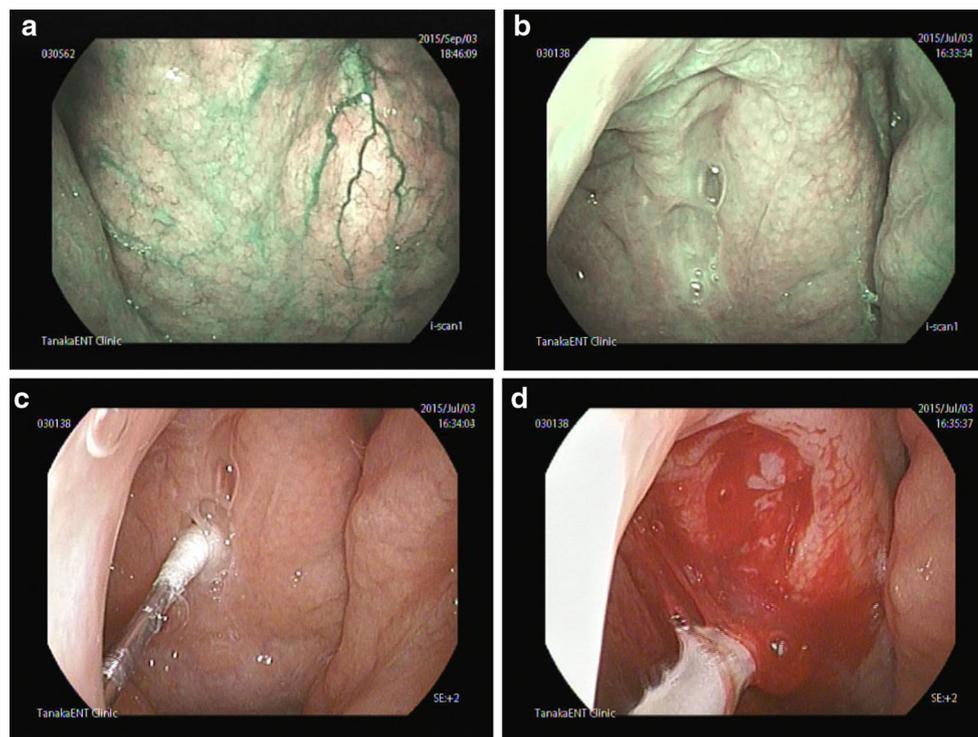


Fig. 2 Endoscopic epipharyngeal findings in normal individual (a) and a representative case of chronic fatigue syndrome/fibromyalgia following HPV vaccination (b–d). The vasculature is clearly distinguishable using optical enhancement mode (a). The vasculature

is not apparent due to submucosal edema and congestion (b), and prone to bleeding on abrasion with a 0.5 % ZnCl₂-soaked cotton swab (c, d) [16]

general, individuals with a heavy smoking habit have more severe chronic epipharyngitis. Both cigarette smoke and air pollution have been reported to be responsible for development of autoimmunity [13–15]. Thus, it is conceivable that various types of autoimmune disease in smokers might be related to accelerated chronic epipharyngitis.

Patients with FSS following HPV vaccination

Between October 2014 and September 2015, we examined the epipharynx in 41 young women of mean 17.3 (range 14–23) years exhibiting chronic fatigue syndrome/fibromyalgia-like symptoms in accordance with FSS following HPV vaccination. They had various symptoms, including headache in 40/41 (97.6 %), general fatigue in 39 (95.1 %), sleep disturbance in 36 (87.8 %), stiffness of neck and upper back in 35 (85.3 %), photophobia in 33 (80.5 %), menstrual disorder in 32 (78.0 %), dizziness in 31 (75.6 %), muscle weakness in 31 (75.6 %), nausea in 30 (73.1 %), cognitive impairment in 28 (68.3 %), tinnitus in 28 (68.3 %), abdominal pain or diarrhea in 27 (65.9 %), generalized pain in 25 (61.0 %), joint pain in 24 (58.5 %), pyrexia in 20 (48.8 %), restless legs in 14 (31.4 %), cough in 12 (29.2 %), and involuntary movement in 11 (26.8 %). As a result, 34 of 41 (82.9 %) patients were unable to attend school.

They had been previously treated using a number of approaches, including steroids, sleep-inducing drugs, anti-anxiety drugs, nonsteroidal anti-inflammatory drugs, vitamins, and biological products. However, their condition had not significantly improved in response to any of these interventions.

Although mild pharyngeal symptoms had been previously noticed in only 19 patients (46.3 %), the 0.5 % ZnCl₂ procedure on the epipharynx revealed that all 41 patients had severe epipharyngitis, identified by severe bleeding at the time of examination.

Sixteen of the 41 patients consented to hospitalization in order to undergo epipharyngeal abrasion with 0.5 % ZnCl₂ solution. For the duration of treatment, all 16 patients stopped receiving any other medication. Marked improvement in symptoms was observed in 13 of 16 patients, with four patients eventually achieving a cure. Given the degree of impairment of quality of life previously observed in these patients, the degree of response to this treatment was quite remarkable. In the remaining three patients, who were not or minimally responsive to treatment, considerable post-abrasive hemorrhages remained at the end of treatment period, indicating ongoing epipharyngitis [16].

The extremely high incidence of severe epipharyngitis and dramatic improvement in FSS concomitant with amelioration of epipharyngitis by ZnCl₂ treatment strongly

suggest that FSS following HPV vaccination may be related to chronic epipharyngitis.

Etiology of FSS following HPV vaccination

Recently, several investigators have expressed mounting concern about development of FSS following vaccinations, including those for HPV and hepatitis B [4–8, 17] characterized by general and multisystem symptoms in the absence of specific clinical manifestations, organic lesions, or pathologic findings [18]. In fact, various symptoms observed in our patients following HPV vaccination seem to be in accordance with FSS. Although a causal association has not been proven, it was recently hypothesized that the development of FSS following vaccination may be triggered by an adjuvant stimulus; the concept of an autoimmune/inflammatory syndrome induced by adjuvant (ASIA) was proposed [19, 20] and a subsequent link between ASIA syndrome and HPV vaccination suggested [21]. Currently approved HPV vaccines contain aluminum, the most widely used adjuvant, which enhances the immune response by affecting both the innate and adaptive immune system [22] and thus raises the possibility of this response causing systemic adverse effects via an effect on systematic actions on immune function. Because the epipharynx is rich in activated lymphocytes [9] and a considerable amount of body fluid is physiologically secreted on the epipharyngeal surface, it is conceivable that latent inflammation of the epipharynx may be prone to exacerbation by an adjuvant stimulus, such as HPV vaccination.

Another mechanism could be that the interaction between the epipharyngeal immune response and FSS is mediated via an impact upon the HPA axis. In addition, cognitive impairment and memory loss, which were frequently observed with FSS following HPV vaccination, suggest that the functional alteration may be not restricted to the hypothalamus but is expanded to the limbic system in some patients. Alteration of the HPA axis has been documented to play an important role in FSS, including chronic fatigue syndrome and fibromyalgia [23, 24] and, interestingly, epipharyngitis has been previously documented to affect the HPA axis [1]. Therefore, we speculate that an improvement in the HPA axis and alteration in the limbic system, which occurs concomitantly with improvement in epipharyngitis in response to treatment with ZnCl₂ may be the underlying mechanism responsible for the amelioration of FSS in our patients. If this is true, there may be wider implications for the treatment of FSS, i.e., a need for resolution of any underlying chronic epipharyngitis.

Taken together, we hypothesize that the adjuvant-induced epipharyngitis and subsequent alteration of the HPA

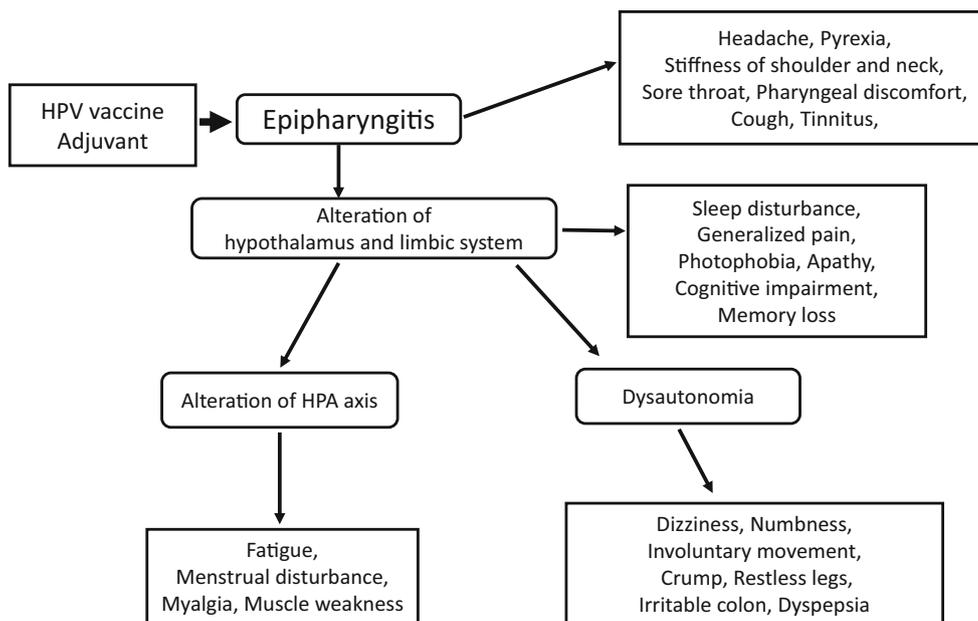


Fig. 3 Hypothetical mechanism of functional somatic syndrome following human papillomavirus vaccination [16]

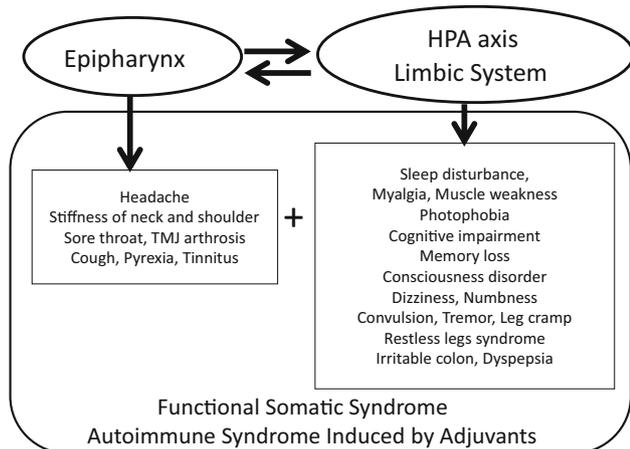


Fig. 4 Epipharynx- HPA/limbic system interaction hypothesis

axis and limbic system may play a central role in the development of FSS following HPV vaccination (Fig. 3).

Epipharynx-HPA axis/limbic system interaction hypothesis

Our observations and those of Horiguchi et al. [1] suggest that chronic epipharyngitis may cause dysfunction in the HPA axis, resulting in the various symptoms observed in FSS patients.

However, among these symptoms in FSS, those symptoms, such as headache, shoulder and neck stiffness, throat

discomfort, cough, pyrexia, tinnitus, and temporomandibular joint disorder could be considered to be symptoms related to chronic pharyngitis rather than dysfunction of the HPA axis. On the other hand, too much stress often causes worsening of chronic epipharyngitis.

Thus, we hypothesize that both the epipharynx and the HPA axis/limbic system influence each other, and that chronic epipharyngitis combined with interactions with the epipharynx-HPA axis/limbic system may play a central role in the development of FSS (Fig. 4).

Conclusion

Chronic epipharyngitis is a long recognized but not widely understood condition. However, it may have an important role in the development of various autoimmune diseases and disorders of the autonomic nervous system, including ASIA.

Further, we suggest that the condition of the epipharynx may be worthwhile examining in the broader context of treatment of autoimmune disease and autonomic nervous disorders regardless of the initial cause.

Given that chronic epipharyngitis is not fully understood, we think that this condition should be an important direction in future research.

Acknowledgments We thank Professors Kensuke Joh and Prof. Yehuda Shoenfeld for their encouragement. We also appreciate Dr. Yoshiteru Aida and Mr. Tatsushi Ohsawa for their contribution to this research.

Compliance with ethical standards

Conflict of interest Osamu Hotta, Ayaki Tanaka, Akira Torigoe, Kazuaki Imai, and Norio Ieiri declare that they have no conflict of interest in this work.

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