

# Clinical and allergological analysis of ocular manifestations of sick building syndrome

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**Purpose:** The disease concept of sick building syndrome (SBS) is still unclear. Ocular mucous membrane irritation is one of the major symptoms of SBS. However, the immunological aspects of the ocular complications of SBS are not yet clarified. The clinical and allergological aspects of SBS cases with ocular disorders with special reference to allergic conjunctival diseases (ACD) were analyzed, especially with respect to local immunological features.

**Methods:** Twelve cases of SBS with ocular findings and 49 cases of ACD (allergic conjunctivitis [AC], atopic keratoconjunctivitis [AKC], and vernal keratoconjunctivitis [VKC]) for comparison were evaluated. The clinical findings in SBS and ACD were scored, and tear film breakup time (BUT) was measured. Cytokine (interferon- $\gamma$  [IFN- $\gamma$ ], interleukin [IL]-2, IL-4, IL-5, IL-6, IL-8, and IL-13) concentrations in tears were analyzed by cytometric bead arrays. Eosinophil count in peripheral blood, total IgE in serum, and multiple allergen simultaneous test (MAST) for antigen-specific IgE were also measured.

**Results:** In SBS, conjunctival lesions were observed in all cases, and corneal abnormalities were found in two-thirds of the cases. Limbal lesions were observed in 2 pediatric cases. Mean serum total IgE level in SBS was significantly higher than that in AC; however, it was significantly lower than that in AKC and VKC. Eosinophil count in peripheral blood and number of positive allergens in MAST were significantly lower in SBS than in AKC and VKC. Significant elevation of tear IL-4 was observed in SBS and ACD. However, in contrast to ACD, elevation of other cytokines in tears was not observed in SBS. Mean tear BUT in SBS was in the normal range.

**Conclusion:** From these results, SBS is thought to be partially induced by an allergic response. However, clinical dissociation of the ocular clinical findings and local immunological features in tear cytokines may suggest that SBS belongs to a different entity from ACD.

**Keywords:** sick building syndrome, allergic conjunctival disease, cytokine, vernal keratoconjunctivitis, IgE

## Introduction

In 1983, the World Health Organization (WHO) used the term “sick building syndrome (SBS)” for the first time to describe situations in which building occupants experience acute effects on health and comfort that appear to be linked to the time spent in a building,<sup>1</sup> and SBS was divided into broad categories of mucous membrane irritation (eyes, nose, and throat irritation), neurotoxic effects (headaches, fatigue, and irritability), asthma and asthma-like symptoms (chest tightness and wheezing), skin dryness and irritation, gastrointestinal complaints, and others,<sup>2</sup> but no specific illness or cause has been identified at present. The United States<sup>3</sup> and Japanese<sup>4,5</sup> governments have introduced environmental indexes for prevention of SBS, and clinical disorders associated with office buildings, houses, and schools have also been frequently recognized as SBS especially in Japan since around 2000.

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Low quality of the indoor environment is associated with very non-specific symptoms affecting the eyes, nose, throat, and skin and general symptoms such as headaches and tiredness, sometimes denoted as SBS.<sup>6</sup> Irritation and dryness of the eyes together with a blocked or runny nose and dry throat are especially considered an important part of the oculonasal mucosal symptoms of SBS.<sup>7</sup> However, although symptoms of SBS occur only in specific buildings or dwellings, they disappear when the individual leaves the environment. Therefore, it is difficult to analyze the clinical and allergological characteristics of SBS, including ocular findings. Factors contributing to perceived indoor air quality include temperature, humidity, odors, air movement, ventilation, bioaerosols, and volatile organic compounds (VOC), such as formaldehyde, xylene, toluene, and methylene chloride.<sup>4,8</sup>

Several studies have reported the prevalence of ocular manifestations in SBS patients.<sup>9–13</sup> In other studies, ocular disorders were analyzed in relation to nasal or respiratory symptoms, with special consideration of the mucosal characteristics of SBS.<sup>14–17</sup> A few past studies focused especially on ocular findings in SBS.<sup>18,19</sup> However, the immunological aspects of ocular complications of SBS have not been reported in detail.

Some studies have suggested an allergological background in SBS,<sup>20,21</sup> but it has been pointed out that chemical, toxic, and neurological features are also important in the pathophysiology of SBS.<sup>22,23</sup> In this study, we report the clinical and allergological aspects of SBS cases with ocular disorders with special reference to allergic conjunctival diseases (ACD: allergic conjunctivitis [AC], atopic keratoconjunctivitis [AKC], and vernal keratoconjunctivitis [VKC]), in order to analyze their similarities and differences, especially with respect to local immunological features.

## Methods

### Study population

This is a consecutive case series study of 12 patients (2 males and 10 females) who attended Yokohama City University Medical Center with SBS symptoms, especially ocular irritation in a specific building (Table 1). They were asked to complete a self-reporting questionnaire survey as previously proposed by Lu et al,<sup>24</sup> and written informed consent was obtained from all patients. SBS symptoms were defined as one or more selected symptoms specified in the questionnaire for at least 1–3 days a week while at work in the office in the previous month, but which improved or disappeared after work or on days without work. The SBS symptoms were identified individually as the following groups: eyes (eye dryness and eye irritation), upper respiratory tract (nasal itching, runny nose, blocked nose, sneezing, and dry throat), lower respiratory tract (difficulty breathing), skin (skin dryness), and non-specific symptoms (headache, tiredness, difficulty concentrating, irritability, and dizziness).<sup>24</sup> Those who had past history of medical treatment for systemic diseases, such as hypertension, cardiac diseases, and hyperthyroidism, were excluded from the study population.

For comparative evaluation with SBS, 49 patients with ACDs who also attended Yokohama City University Medical Center were included in this study. ACD was classified into AC, AKC, or VKC according to the guidelines for the diagnosis and treatment of conjunctivitis, and past reports.<sup>25,26</sup> The ACD patients consisted of 14 with AC, 14 with AKC, and 21 with VKC. Normal (non-allergic) subjects were subjected to immunological testing for comparison. This study was approved by Yokohama City University Medical Center Review Committee of Clinical Research.

**Table 1** Cases of sick building syndrome

No	Age	Sex	Place where symptom occurred	Conjunctival lesion score	Corneal lesion score	Limbal lesion score	Clinical type
1	7	F	School	1	1	1	VKC
2	8	M	School	1	1	1	VKC
3	27	F	English conversation school	3	1	0	AC
4	34	F	Underground shopping arcade	1	1	0	AC
5	34	F	Own house	3	0	0	AC
6	41	F	Own house	2	0	0	AC
7	41	M	Company building	1	1	0	AC
8	43	F	Own house	2	1	0	AC
9	47	F	Supermarket	2	0	0	AC
10	54	F	Own house	1	0	0	AC
11	55	F	Subway station	2	1	0	AC
12	57	F	Sports gym	2	1	0	AC

**Note:** Clinical evaluation of ocular findings was carried out according to the ocular clinical grading system reported previously,<sup>26</sup> and conjunctival, corneal, and limbal scores were summed.

**Abbreviations:** F, female; VKC, vernal keratoconjunctivitis; M, male; AC, allergic conjunctivitis.

## Clinical grading

Clinical evaluation of ocular findings was carried out according to the ocular clinical grading system reported previously.<sup>26</sup> Ocular findings of slit lamp examination were recorded on the patients' first visit to our outpatient clinic. Ten objective ocular clinical findings of conjunctival, limbal, and corneal lesions were graded on a 4-point scale (0= none, 1= mild, 2= moderate, and 3= severe; left and right eyes separately in each case). The total score of 10 findings, with a maximum of 30, taking the score of the more severe side in bilateral cases, was used as the clinical score.

## Serological analysis

Serum total IgE level, eosinophil count in peripheral blood, and multiple allergen simultaneous test (MAST) for antigen-specific IgE were measured in each case.

## Tear cytokine analysis

Tear fluid was extracted by the Schirmer method, as previously described, when the subjects attended our clinic.<sup>27</sup> All samples were rapidly frozen at  $-20^{\circ}\text{C}$  and maintained at  $-80^{\circ}\text{C}$  until cytokine analysis. Tear fluid extraction was performed with 0.5 M NaCl and 0.5% Tween 20 in 0.01 M phosphate buffer (pH 7.2). The cytokine composition of tears was analyzed using a BD™ (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) Cytometric Bead Array system and a flow cytometer (BD™ FACS Canto II), according to the manufacturer's instructions. Data were acquired and analyzed using FCAP Array™ software (Version 1.0.1; BD Biosciences, Tokyo, Japan). Standard curves were generated using the reference cytokine concentrations supplied by the manufacturer. The following 7 inflammatory cytokines were analyzed: interferon- $\gamma$  (IFN- $\gamma$ ), interleukin (IL)-2, IL-4, IL-5, IL-6, IL-8, and IL-13.

## Tear film breakup time (BUT)

The time from the conclusion of a blink to the occurrence of tear film fracture (BUT) was observed and recorded in SBS cases using a non-invasive method with slit lamp microscopy as reported previously.<sup>28</sup>

## Statistical analysis

Since it has not been established whether the clinical score of ACD shows a normal distribution, non-parametric analysis was conducted in this study. The Mann-Whitney *U* test was used to identify differences among patient groups. A independent *t*-test for independent groups with unequal variance was also adopted. A *P*-value of  $<0.05$  was accepted as statistically significant.

**Table 2** Sex and age distribution of each disease

Disease	Male:female	Age (mean $\pm$ standard deviation)
SBS	2:10	37.3 $\pm$ 16.6
AC	6:8	28.9 $\pm$ 14.5
AKC	6:8	27.1 $\pm$ 13.6
VKC	16:5	18.0 $\pm$ 5.8**
Normal controls	5:8	31.2 $\pm$ 10.2

**Note:** \*\* $P < 0.01$  vs SBS independent (*t*-test).

**Abbreviations:** SBS, sick building syndrome; AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis.

## Results

Demographic profiles of the SBS cases in this study are shown in Table 1. Middle-aged female patients comprised the majority of cases in this series. Most patients noticed their symptoms in closed spaces or poorly air-conditioned spaces. Conjunctival lesions were observed in all cases, and corneal abnormalities were found in two-thirds of cases. Two pediatric cases showed limbal proliferative change. SBS cases were older than ACD patients, with a significant difference between SBS and VKC ( $P < 0.05$  in independent *t*-test for independent groups with unequal variance; Table 2).

Mean clinical score of conjunctival changes in SBS was significantly lower than that in AC and VKC. Mean corneal score in SBS was significantly higher than that in AC, but significantly lower than that in VKC. Mean limbal lesion score in SBS was significantly lower than that in VKC. Mean total clinical score in SBS did not show a significant difference from that in AC and AKC, but that in VKC was higher than that in SBS (Mann-Whitney *U* test; Table 3). Adult cases of SBS showed similar clinical features of AC, thus comparison between AC type of SBS and AC was conducted; however, the difference was similar to that of whole SBS (data not shown).

Mean serum total IgE level in SBS was significantly higher than that in AC, but was significantly lower than that in AKC and VKC. Eosinophil count in peripheral blood and

**Table 3** Clinical scores of ocular findings

Location of lesions	SBS	AC	AKC	VKC
Conjunctival lesions	1.75 $\pm$ 0.75	2.64 $\pm$ 0.84*	2.29 $\pm$ 1.14	13.7 $\pm$ 2.96*
Corneal lesions	0.67 $\pm$ 0.49	0.07 $\pm$ 0.27**	0.36 $\pm$ 0.50	2.05 $\pm$ 0.97**
Limbal lesions	0.17 $\pm$ 0.39	0	0	1.95 $\pm$ 2.08**
Accumulated clinical score	2.58 $\pm$ 0.79	2.71 $\pm$ 0.82	2.64 $\pm$ 1.33	17.7 $\pm$ 4.29#

**Notes:** Values are mean  $\pm$  standard deviation. \* $P < 0.05$ , \*\* $P < 0.01$ , and # $P < 0.001$  vs SBS (Mann-Whitney *U* test).

**Abbreviations:** SBS, sick building syndrome; AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis.

**Table 4** Serological analysis

Tested item	SBS	AC	AKC	VKC
Serum total IgE (IU/mL)	136±96.3	40.0±45.2**	5,340±5,757**	2,630±3,690**
Peripheral blood eosinophil count (%)	2.85±1.77	3.33±1.95	7.69±3.12 <sup>#</sup>	7.77±3.40 <sup>#</sup>
Number of MAST-positive antigens	1.08±0.90	1.42±0.85	5.57±1.70	3.95±1.96

**Notes:** Values are mean ± standard deviation. Serum total IgE was analyzed by independent t-test. Other items were evaluated by the Mann–Whitney U test. \*\**P*<0.01 and <sup>#</sup>*P*<0.001 vs SBS.

**Abbreviations:** SBS, sick building syndrome; AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis; MAST, multiple allergen simultaneous test.

number of positive allergens in MAST were significantly lower in SBS than in AKC and VKC (Table 4).

Analysis of tear cytokine levels showed no statistically significant difference in IFN- $\gamma$  and IL-2 between normal controls and any disease group. Tear IL-4 level was significantly elevated in all groups compared with controls. Tear IL-5, IL-6, and IL-8 levels in patients with VKC were significantly higher than those in normal controls, and that of IL-13 in AKC and VKC was significantly higher than that in normal controls, but such elevation was not observed in SBS (Table 5).

BUT in SBS cases was 12.1±3.1 seconds (mean ± standard deviation), meaning that SBS cases with ocular signs had normal lacrimation function. In these cases, the prevalence of SBS symptoms calculated based on a self-reporting questionnaire survey was as follows: 100% of participants had eye symptoms, 75% had upper respiratory symptoms, 33% had lower respiratory symptoms, and 67% had non-specific symptoms. Tiredness (42%), headache (58%), and difficulty concentrating (17%) were reported.

## Discussion

This study showed that most cases were older than 40 years and were female, similar to past studies.<sup>10,13,14</sup> It is basically recognized that symptoms of SBS are only observed in a specific building and that they disappear outside the building. However, some objective clinical findings can be observed in the clinic far away from the causal building.

It is considered that some clinical changes in SBS might be irreversible due to pathological conditions. However, upon comparing the clinical ocular findings of SBS with those in ACD, conjunctival change was milder, and corneal change seemed to be more severe in the present study. It is difficult to explain the reason for these findings. From the allergological standpoint, it might be possible that the fact that the clinical and immunological surveys were conducted outside the specific building might have impaired the detection of early-phase reaction-induced changes in this study. In contrast to conjunctival findings, corneal and limbal lesions are considered to be affected by local invasion of eosinophils in the late phase reaction, thus explaining that the ocular findings observed in the clinic might have been induced by SBS.<sup>29</sup> A VOC exposure study might be meaningful for direct clinical observation of ocular findings, but this type of experimental equipment is restricted in Japan at present.<sup>30</sup> Experimental exposure to airborne office dust was conducted and analyzed in humans, and it was reported that irritative mucosal symptoms appeared.<sup>16</sup> However, VOC were not evaluated in this study.<sup>16</sup>

The absence of an elevation of peripheral blood eosinophil count in SBS cases seems to be inconsistent with a previous study in which eosinophil count in peripheral blood was a predictor of SBS.<sup>31</sup> However, the fact that a small proportion of patients exhibited serious systemic complaints in contrast to ocular changes might suggest that local ocular lesions hardly affected systemic eosinophil count in this study,

**Table 5** Comparison of tear cytokines

Biomarker	SBS	AC	AKC	VKC	Normal controls
IFN- $\gamma$ (pg/mL)	97.0±67.0	101±137	111±72.4	101±44.9	91.7±31.2
IL-2 (ng/mL)	25.0±28.6	75.7±122	74.3±162	124±247	36.8±111
IL-4 (fg/mL)	1.07±1.23*	0.34±0.45*	1.44±2.35*	1.66±2.83*	0.06±0.16
IL-5 (pg/mL)	42.7±32.8	73.9±57.1	104±112	256±194 <sup>#</sup>	40.2±28.9
IL-6 (pg/mL)	15.8±15.8	11.5±11.1	21.2±22.8	48.2±38.3 <sup>#</sup>	8.3±8.3
IL-8 (pg/mL)	9.4±14.0	34.4±25.3	66.8±59.9	132±113**	31.9±43.5
IL-13 (pg/mL)	5.54±6.61	6.96±6.67	20.5±11.2 <sup>#</sup>	16.4±14.8 <sup>#</sup>	3.38±3.67

**Notes:** Values are mean ± standard deviation. Statistical analysis was carried out with independent t-test. \**P*<0.05, \*\**P*<0.01, and <sup>#</sup>*P*<0.001 vs normal controls.

**Abbreviations:** SBS, sick building syndrome; AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis; IFN- $\gamma$ , interferon- $\gamma$ ; IL, interleukin.

and further investigation will be necessary. We observed 2 pediatric cases, who complained of irritative symptoms at school, and it is interesting that their findings included limbal proliferative change, which is specific to VKC. The reason why pediatric cases exhibited more serious ocular changes than those in adult cases is unclear, but a recent study revealed age-related changes in conjunctival structure,<sup>32</sup> leading to the assumption that an immature conjunctival structure might induce those specific clinical characteristics that resemble VKC. However, it is not denied that pediatric SBS patients with ocular symptoms are complicated with VKC. Limbal type of VKC is a minor spectrum in VKC whose pathological mechanism is not clarified at present, and further investigation is also needed.

From the evaluation of tear cytokine levels, the significant elevation of IL-4 (a Th2-type cytokine) and the absence of significant change in IL-2 or IFN- $\gamma$  (Th1-type cytokines) levels in SBS strongly reflect the presence of allergic reaction in the ocular surface of SBS patients. However, considering the lower levels of serum total IgE and inflammatory tear cytokines in SBS compared to ACD, and the fact that limbal proliferative change is found only in pediatric cases of SBS, the ocular lesions in SBS can hardly be categorized in the same spectrum as ACD, because in our past study, we reported that the ocular clinical grading system had sufficient sensitivity to differentiate each disease within ACD, such as AC vs VKC.<sup>26</sup>

Regarding BUT in SBS cases, no significant change was observed in our study. Several studies have reported a significant decrease in BUT in SBS cases,<sup>16,17</sup> but BUT was also reported to increase only at higher night air temperatures in another study.<sup>9</sup> Because a significant decrease in BUT was observed in an experimental air-borne exposure study in which office dust was used,<sup>16</sup> BUT value might be affected by different test circumstances. From these controversial results, it is considered that multiple elements and air status affect the result of BUT. In this study, BUT was carried out only in SBS cases due to the study design, and recent studies mentioned that the incidence of dry eyes has increased in patients with ACD.<sup>33,34</sup> It is estimated that chronic pathological change seems to affect the ocular surface, leading to abnormalities in tear film stability, epithelial cells integrity, and corneal nerve function in ACD,<sup>31</sup> whereas this pathophysiological feature cannot be applied to SBS because of its basically reversible nature.

The limitations of this study were as follows: this study was designed from the standpoint of ophthalmological aspects of SBS; thus, the study population was small, and

unlike in cross-sectional studies based on populations in office buildings, multiple logistic regression analysis was impossible in our study. Measurement of environmental parameters using calibrated instruments for each patient was not done because of the restriction of laboratory equipment and considerable diversity in the specific location of each patient. The causal elements might vary in each case, such as VOC, odors, dust, and bioaerosols. Systemic features were only collected from self-reporting questionnaires, and medical examination was not carried out because most patients only suffered ocular symptoms that did not require systemic medical treatment.

## Conclusion

Few studies have investigated the ocular symptoms in SBS, and little is known about the clinical and pathological properties of SBS, especially its ocular lesions. We report that the ocular changes in SBS have allergological characteristics, but the existence of several findings that are not similar to conventional ACD also suggest that further investigation is needed for proper orientation of SBS with allergic diseases.

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## Disclosure

The authors report no conflicts of interest in this work.

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