Present state of Japanese cedar pollinosis: The national affliction

Takechiyo Yamada, MD, PhD,[a] Hirohisa Saito, MD, PhD,[b] and Shigeharu Fujieda, MD, PhD[a] *Fukui and Tokyo, Japan*

Seasonal allergic rhinitis (SAR) caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) is the most common disease in Japan and has been considered a national affliction. More than one third of all Japanese persons have sugi-pollinosis, and this number has significantly increased in the last 2 decades. In our opinion the reason why sugi-pollinosis became a common disease in the last half century is the increased number of cedar pollens, with global climate change and forest growth caused by the tree-planting program of the Japanese government after World War II playing substantial roles; dust storms containing small particulate matter from China might also contribute to the increased incidence of sugi-pollinosis. To help minimize their symptoms, many Japanese wear facemasks and eyeglasses at all times between February and April to prevent exposure to JCP and aerosol pollutants. Forecasts for JCP levels typically follow the weather forecast in mass media broadcasts, and real-time information regarding JCP levels is also available on the Internet. Because a large amount of JCP is produced over several months, it can induce severe symptoms. Japanese guidelines for allergic rhinitis recommend prophylactic treatment with antihistamines or antileukotrienes before the start of JCP dispersion. Additionally, sublingual immunotherapy will be supported by health insurance in the summer of 2014. However, many patients with sugi-pollinosis do not find satisfactory symptom relief with currently available therapies. Collaboration between scientists and pharmaceutical companies to produce new therapeutics for the control of sugi-pollinosis symptoms is necessary. (J Allergy Clin Immunol 2014;133:632-9.)

Key words: *Seasonal allergic rhinitis, Japanese cedar, global climate change, prophylactic treatment, alternative complementary treatments*

Allergic rhinitis (AR) represents a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life (QOL) in persons of all ages. In the Allergic Rhinitis and its Impact on Asthma study, AR is divided into 2 categories: intermittent or persistent disease.[1] However, many otorhinolaryngologists in Japan use a perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) classification system.[2] The major allergen contributing to SAR in Japan is pollen from the Japanese cedar (*Cryptomeria japonica*; ie, sugi). SAR is caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) and was first reported in 1963.[3] During the height of the allergy season (between February and April), a large number of patients with sugi-pollinosis experience more severe symptoms for longer periods of time compared with other pollen allergies (Fig 1, *A*). This might be because JCP is dispersed in large quantities over long distances (>100 km in some cases) and can remain airborne for more than 12 hours (Fig 1, *B*).[4] Furthermore, pollen from the Japanese cypress *(Chamaecyparis obtusa)*, which also causes SAR, is dispersed in April and May, immediately after the release of JCP. Because Japanese cypress pollens are considered to contain several components that cross-react with JCP, 70% of patients with sugi-pollinosis also experience SAR caused by Japanese cypress pollen. Therefore allergic symptoms can last for as long as 4 months, from February to May, with some variation caused by annual climate differences.

A meta-analysis of 38 reports representing 27 prevalence subgroups and 134 sensitization rate subgroups showed that the prevalence of sugi-pollinosis increased 2.6-fold between 1980 and 2000.[5] The prevalence of sugi-pollinosis was 19.4% of the Japanese population in 2001.[6] We conducted a survey of 1540 persons aged 20 to 49 years in Fukui City between 2006 and 2007 that indicated the positive rate of serum JCP-specific IgE was 56.3% and the prevalence of sugi-pollinosis was 36.7%.[7] Additionally, the International Study of Asthma and Allergies in Childhood showed that Tokyo schoolchildren have an extremely high prevalence of SAR.[8,9] Specific to Japan, SAR-JCP is now called a national affliction. Manufacturers and

From [a]the Department of Otorhinolaryngology–Head & Neck Surgery, University of Fukui, and [b]the Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo.

Supported by Grants-in-Aid for Scientific Research from the Japanese Ministry of Health, Labour and Welfare (H23-Immunology-general-006) and from the Japanese Ministry of Education, Culture, Sports, Science and Technology (23390397, 22659306).

Disclosure of potential conflict of interest: T. Yamada is employed by the University of Fukui and has received research support from the Japanese Ministry of Health, Labour, and Welfare. H. Saito is employed by the National Center for Child Health and Development; has received research support from the Japanese Ministry of Health, Labour, and Welfare; has received payment for lectures from Teijin Pharma, Shiseido, Merck Sharp and Dohme K.K., Taiho Pharmaceutical, Nippon Boehringer-Ingelheim, Ono Pharmaceutical, GlaxoSmithKline K.K., Pfizer Japan, and Novartis Pharma K.K.; has received payment for manuscript preparation from Taiho Pharmaceutical; has received payment for development of educational presentations from Shimane University and Toho University; and has received travel support from Shimane University Japanese Society of Allergology, the Japanese Society of Pediatric Allergy & Clinical Immunology, and Pfizer Japan. S. Fujieda has received research support from the Japanese Ministry of Health, Labour, and Welfare, the Japanese Ministry of Education, Culture, Sports, Science and Technology, Ono Pharmaceutical, and Merck Sharp & Dohme K.K.; has consultant arrangements with Kyorin Pharmaceutical; is employed by the University of Fukui; and has received payment for lectures from Kyowa Hakko Kirin, Ono Pharmaceutical, and Merck Sharp & Dohme K.K.

Received for publication July 17, 2013; revised November 6, 2013; accepted for publication November 7, 2013.

Available online December 19, 2013.

Corresponding author: Shigeharu Fujieda, MD, PhD, Department of Otorhinolaryngology–Head & Neck Surgery, University of Fukui, 23-3 Matsuoka-Shimoaizuki, Eiheiji, Yoshida, Fukui 910-1193, Japan. E-mail: sfujieda@u-fukui.ac.jp.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.11.002

Abbreviations used

AD: Asian dust
apoA-IV: Apolipoprotein A-IV
AR: Allergic rhinitis
GWAS: Genome-wide association study
JCP: Japanese cedar pollen
PAR: Perennial allergic rhinitis
PM: Particulate matter
PM2.5: Particulate matter less than 2.5 μm in diameter
QOL: Quality of life
SAR: Seasonal allergic rhinitis
SLIT: Sublingual immunotherapy
Sugi-pollinosis: Seasonal allergic rhinitis caused by Japanese cedar

retailers are set to tap into a soaring demand for medications and related items, and the market for JCP prescription drugs has soared to 200 to 300 billion yen per season (2.1-3.2 billion US dollars). Also, the government will be required to take effective actions.

In this review we introduce sugi-pollinosis, the national affliction of Japan, with the intention of informing allergists about the spectrum of symptoms and treatment options available for patients with sugi-pollinosis.

PUTATIVE TRIGGER FACTORS, ENVIRONMENT, AND PATHOLOGY FOR THE INCREASED PREVALENCE OF SUGI-POLLINOSIS

In Japan forests cover approximately 25 million hectares (ie, 66% of the total area of Japan). More than half of these trees were planted from the early 1950s to the early 1970s, and according to the Forestry Agency of Japan, an estimated 4.6 billion of these are Japanese cedar trees, covering nearly 18% of the total land area of Japan. The sugi trees are extremely straight and tall, making them ideal construction materials, but after wood tariffs decreased in 1964, imported wood put the sugi foresters out of business, and most sugi trees have been abandoned and grow taller and produce more pollen each year. With the exception of Hokkaido and Okinawa islands, this yellow-green dust is scattered throughout Japan. Airborne JCP levels have been monitored in Sagamihara hospital (Kanagawa, Japan) since 1965. JCP counts can vary significantly from year to year because of weather conditions; however, the total JCP counts from 1995 to 2013 have been significantly greater than those in the initial period from 1965 to 1994 ($P < .05$; Fig 2, *A*).

Epidemiologic studies have demonstrated that global climate change correlates with the number of symptomatic pollen-induced respiratory allergies and allergic diseases.[10,11] One of the fundamental effects of climate change is the potential for shifts in flowering phenology and pollen production associated with warmer seasonal air temperatures. As such, the length of the sugi-pollinosis season has increased since 1995.[12] Although the average global temperature has only increased by approximately 0.6°C in the 20th century, climate change in Japan has been more severe, with temperatures increasing by an average of 1.15°C in the past 100 years. Fig 2, *B*, shows the annual temperature change since 1960 in Japan.

Cedar pollen is released from male flowers on sugi trees (Fig 1, *C*). Hot summers usually affect sugi trees, promoting flower bud development and increasing pollen production; meanwhile, cool summers have opposite effects. Ito et al[13] investigated the correlation between total JCP count and the previous years' summer weather conditions from 1987 to 2006. The annual cumulative level of airborne JCP was significantly related to the mean temperature and sunlight hours in late July before the start of the pollen season (see Table E1 in this article's Online Repository at www.jacionline.org). The mean temperature in July during the 20th century has also significantly increased in Japan. Average temperatures in the Fukui area from 1974 to 1993 and 1994 to 2012 were 25.1°C ± 0.3°C and 26.2°C ± 0.3°C, respectively ($P < .05$; Fig 2, *C*). The weather of late winter and early spring was not correlated with JCP counts; however, temperatures in January and February did influence the start of sugi pollen production and the pollen season (data not shown).

JCP counts were significantly associated with the prevalence of sugi-pollinosis. The mean JCP count in the mountainous area of Akita prefecture was 2 times higher than that in the coastal area of Akita from 1996 to 2006 (see Table E2 in this article's Online Repository at www.jacionline.org). The prevalence of sugi-pollinosis in children (age, 10-11 years) in 2006 was higher in mountainous areas than in coastal areas, although the prevalence of PAR was not different between the 2 areas (see Table E3 in this article's Online Repository at www.jacionline.org). The positive rate of serum anti-JCP–specific IgE in the mountainous area was also higher than in that in the coastal areas, but the positive rate of anti-mite IgE did not increase in the mountainous area.[14]

Asian dust (AD) and urban particulate matter (PM) are risk factors for sugi-pollinosis. AD storms originating in the deserts of Mongolia, northern China, and Kazakhstan are seasonal phenomena that affect much of Eastern Asia, including Japan, and occasionally spread around the globe, affecting the United States as well.[15] The number of spring dust storms has increased in the last 13 years. The frequency of the storms combined with increases in airborne pollution has led to an increase in the adverse effects of the storms. AD contains pollutants, such as sulfur dioxide and nitrogen dioxide, which stimulate immune cells through oxidative stress, enhancing inflammation-related cytokines.[16] AD enhanced nasal allergic reactions induced by repeated JCP administration in guinea pigs.[17] In fact, allergic symptoms have increased during AD storm events in Japan and Taipei.[18,19] Administration of AD plus allergen induced allergen-specific IgE production in mice,[20] suggesting that AD can bind to JCP and induce JCP sensitization in nonatopic or unsensitized atopic subjects.

The main pollutant in Japanese cities is fine PM. Particulate matter less than 2.5 μm in diameter (PM2.5) is frequently reported in spring. PM2.5, a component of AD, induced asthma and enhanced sneezing and rhinorrhea in a manner of type I allergy.[21] Beijing has also recorded its worst levels of air pollution in recent years, and the onset and sensitization of sugi-pollinosis could be easily induced by PM2.5 from China. Environmental authorities in Japan, the United States, and other nations have adopted strict regulations to control PM levels. A wave of criticism, both at home and abroad, prompted Chinese officials to set their own standards in February 2012; however, air quality in China still remains an issue.

GENETIC FACTORS

Genome-wide association studies (GWASs) and meta-analyses of GWASs have shown both common and distinct pathways that