Occupational asthma in Japan

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Research into occupational asthma (OA) in Japan has been led by the Japanese Society of Occupational and Environmental Allergy. The first report about allergic OA identified konjac asthma. After that, many kinds of OA have been reported. Cases of some types of OA, such as konjac asthma and sea squirt asthma, have been dramatically reduced by the efforts of medical personnel. Recently, with the development of new technologies, chemical antigen-induced asthma has increased in Japan. Due to advances in anti-asthma medication, control by medical treatment tends to be emphasized and the search for causative antigens seems to be neglected. Furthermore, we do not have a Japanese guideline for diagnosis and management of OA. This article discusses the current state of OA in Japan.

Key words: Occupational asthma; Allergic asthma; Environment; Workplace

INTRODUCTION

Occupational asthma (OA) has become one of the most common forms of occupational lung disease in many industrialized countries, and it accounts for 9 to 15% of adult asthma [1]. When drug treatment is provided to asthma patients without education to avoid workplace antigen exposure, their symptoms and decline of lung function become fixed and progress to intractable asthma is likely. Therefore, doctors should always take the possibility of OA into consideration and obtain a detailed history. When OA is diagnosed, patients should avoid antigen exposure and the workplace environment should be improved, as well as adequate drug therapy being provided. This article covers the history, current state, and problems related to OA in Japan.

History

The first case of OA in Japan was reported by Seki et al. [2] in 1926 in The Journal of the Japanese Society of Internal Medicine as “Asthma attack induced by working with American red cedar wood.” Large amounts of American red cedar were imported for reconstruction after the Great Kanto Earthquake, and carpenters suffered from asthma when processing this cedar. Similar case reports followed from Tagawa (1929), Shimizu (1929), and Suzuki (1934), while an epidemiological study revealed that approximately 10% (500/5,000) of carpenters were suffering from OA due to cedar. Therefore, import of this cedar was stopped and such OA was no longer seen [3]. After that, there were some case reports about asthma among employees of the sericulture industry. At the same time, the concept of atopy was proposed and the Prausnitz-Küstner (P-K) reaction was discovered (both in

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http://apallergy.org
IgE was discovered in 1966 and the radioallergosorbent test (RAST) method was developed in 1967. After that, OA began to be studied from an immunological perspective. The first example to be identified in Japan was konjac asthma. At that time, bronchial asthma apparently caused by “Maiko” powder was known among the residents living near konjac milling plants and the employees of these plants. A group from the First Department of Internal Medicine at Gunma University (including Shichijo) conducted a detailed field survey in Shimonita that identified OA induced by inhaling Maiko powder, which they called konjac asthma and reported in 1951 [4]. After that, sea squirt asthma, silkworm phosphorus hair asthma, buckwheat asthma, silkworm cocoon asthma, and shiitake mushroom asthma were reported in 1996, 1996, 1970, 1971, and 1985, respectively. Cases of OA have mainly been reported at conferences on occupational allergy (presently, the Japan Society of Occupational and Environmental Allergy) [5]. In the past, most OA occurred among workers engaged in agriculture, fishing, and forestry, with high molecular weight organic substances as the causative antigens. More recently, there has been an increase of OA caused by mineral antigens such as chemicals.

The Japanese Society of Occupational and Environmental Allergy has led the study of OA in Japan up to now. The society was established as the Japanese Conference of Occupational Allergy in 1970. Kojiro Shichijo (Professor of the First Department of Internal Medicine at Gunma University) held the 1st conference at Minakami in Gunma Prefecture. After that, an annual meeting was held in July until 1992. This was the early period for research on occupational allergic diseases in Japan. A number of new occupational allergic diseases were reported at the conferences and members studied the reported cases from the perspectives of both allergy and immunology. The Conference then developed into a new Japanese Society of Occupational Allergy that also included researchers in the field of occupational medicine and public health, and the first congress was held by Prof Nakazawa at Maebashi (Gunma) in 1993. With the growing interest in environmental issues, research into the influence of environmental factors, such as sand, air pollution, and diesel fuel, on allergic diseases was added. The Society was then renamed the Japanese Society of Occupational and Environmental Allergy. Its first congress was held by the president, Professor Ikezawa, in 2002 at Yokohama and it has continued up to the present.

Features and epidemiology of OA in Japan

The causative antigens of OA used to mainly be high molecular weight compounds such as plant and animal products, but non-immunologic asthma induced by exposure to low molecular weight substances such as chemicals has been recognized in recent years [1]. This article is focused on allergic asthma induced by a mechanism based on IgE.

OA accounts for about 15% of adult asthma in Europe and the United States [1]. However, it is difficult to estimate the prevalence of OA precisely because there have been no large-scale epidemiological studies. OA is assumed to account for 2 to 16% of all asthma patients and for about 15% of asthma in adult men. Since it is possible that many patients are treated for asthma without OA being diagnosed, the actual prevalence is probably higher.

Among persons involved in specific types of work, the prevalence of OA depends on the antigens to which they are exposed or the work environment and there are many reports about its prevalence (Table 1) [1, 6]. It is interesting that a high prevalence was reported around some factories because antigens released from the workplace cause residents living around the plants to develop asthma. We found that many residents living around a konjac factory had asthma and we proposed that this should be called “environmental asthma” (Table 2) [6].

Major causative antigens

The causative antigens are varied and sometimes unexpected. The main substances that have been reported in Japan are summarized in Table 3 [6]. Causative agents have become more complex with the development of new industries. The incidence of asthma induced by traditional plant and animal antigens, such as konjac, flour, American red cedar, mushroom spores, sea squirts, and silkworms, is decreasing. On the other hand, asthma induced by chemicals and metals is increasing and has become a serious problem. High molecular weight antigens such as the pollen of vegetables and fruits or spores of mushrooms have become causative antigens along with the increase of greenhouse culture. Various antigens listed in Table 3 such as shiitake mushroom, tomato, and strawberry were not recognized as causing asthma when open field cultivation was common.

Examples of OA in Japan

Konjac asthma

1) Konjac asthma: Bronchial asthma that seemed to be
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Table 1. Estimated prevalence of work-related asthma from cross-sectional studies

| Type of Work                                      | Prevalence (%) | Countries   |
|--------------------------------------------------|----------------|-------------|
| konjac maker                                     | 5.0            | Japan       |
| sericulturist                                    | 9.0            | Japan       |
| polyurethane industry worker,                    | 16.4           | Japan       |
| worker in plastic greenhouses of strawberry      | 4.6            | Japan       |
| worker in plastic greenhouses of shiitake mushroom| 5.0            | Japan       |
| Domestic cleaning                                | 25.0           | Western countries [1] |
| Florists                                         | 14.1           | Western countries [1] |
| Rat allergens                                    | 4.4            | Western countries [1] |
| Natural rubber latex                             | 7.1            | Western countries [1] |
| Supermarket bakery workers                       | 9.0            | Western countries [1] |
| Isocyanates, painters                            | 7.1            | Western countries [1] |

Table 2. The number of Konjac asthma patients around the factories

| Distance from factories | The number of patients (Konjac asthma) | The number of patients (not related to Konjac) |
|-------------------------|----------------------------------------|-----------------------------------------------|
| With in 300 m            | 46                                     | 17                                            |
| 300-1,000 m             | 4                                      | 13                                            |
| More than 1,000 m       | 1                                      | 20                                            |

triggered by Maiko was known among the residents near the konjac milling plant and its employees. The group from the First Department of Internal Medicine at Gunma University performed a detailed field survey at Shimonita in Gunma that identified asthma induced by inhaling Maiko powder, and they named this type of OA as “konjac asthma” and reported it in 1951 [4]. Konjac root is dried and ground into powder in the process of manufacturing the food known as konjac. Maiko is a fine konjac root powder that is blown by air pressure to obtain konjac powder for commercial use. Much of the Maiko powder is dispersed in the air and induces asthma in the plant workers by inhalation. The prevalence of konjac asthma was 16.6% among employees in konjac mills and the age of onset was mostly under 30 years [3].

2) Antigen: The purified antigen named Ag40D-2 is an acidic protein of about 24,000 daltons. Its ratio of basic to acidic amino acids is 1:3.7 and it induces a strong P-K reaction [7]. The amino acid composition of this antigen has also been determined [3, 8].

3) Specific IgE antibody: The immediate skin reaction to a purified Maiko powder antigen is positive in 100% of konjac asthma patients, but negative in non-konjac asthma patients. Konjac asthma patients always show a positive inhalation challenge test with Maiko powder, while control subjects are negative in all cases.

4) Hyposensitization therapy: When this type of asthma was discovered, konjac making was a key industry in the Shimonita area and 40% of the population were involved in producing konjac flour. Specific hyposensitization therapy was developed because of the difficulty in changing jobs. When its efficacy was assessed, it was remarkably effective in 6/35 persons (17.1%) and was effective in 18 (51.4%). The effect of hyposensitization therapy appeared after six months in early cases and after one year in most cases.

Sea squirt asthma

1) Sea squirt asthma is triggered by the inhalation of fluid from protochordate sea squirts that is adherent to cultured oysters [9]. Cultivation of oysters in the Hiroshima region has been done for 400 years and many people are engaged in the task of oyster husking. There were no reports before the second world war, but, employees complained of the onset
### Table 3. Reported occupational antigens in Japan

| Antigen                                      | Occupation                                      | Reference  |
|----------------------------------------------|-------------------------------------------------|------------|
| Plants                                      | Cereal                                          |            |
| Amorphophallus konjac                      | Konjac maker                                    | 1951 Shichijo |
| Buckwheat                                   | Buckwheat miller                                | 1971 Nakamura |
| Wheat flour                                 | Baker                                           | 1971 Jyo   |
| Barley flour                                | Miller                                          | 1991 Noda  |
| Feedstuff (alfalfa, corn)                   | Stock farmer                                    | 1970 Okumura |
| Rice bran                                   | Rice miller                                     | 1977 Makino |
| Wood particle                               | Western red cedar                               | 1926 Seki  |
| Zelkova                                     | Wood processing industry worker                 | 1982 Katsuya |
| Mulberry                                    | Furniture making industry worker                | 1969 Nakamura |
| White birch                                 | Wood processing worker                          | 1979 Takamoto |
| Lauan                                       | Wood processing worker                          | 1968 Aoki  |
| Quince                                      | Wood processing worker                          | 1975 Takahashi |
| Boxwood                                     | Wood processing worker                          | 1985 Tawara |
| Others                                      | Coffee beans podew                              | 1985 Shirakawa |
| Cottonseed                                  | Confectioner                                    | 1985 Ikemori |
| Sesame                                      | Manufacturing plant worker                      | 1990 Tadokoro |
| Tea-leaf                                    |                                                 |            |
| Fresh top                                   | Tea picking worker                              | 1976 Ebihara |
| Component of tea-leaf                       | Tea manufacture worker                          | 1989 Otsuka |
| Fuzz of chrysanthemum                       | Worker in plastic greenhouses                   | 1969 Suga  |
| Tomato (component in stalk)                 | Worker in plastic greenhouses                   | 1980 Saito |
| Lettuce (component in stalk)                | Worker in plastic greenhouses                   | 1980 Saito |
| Fuzz of melon                               | Worker in plastic greenhouses                   | 1980 Masuyama |
| Indian rice                                 | Wood processing worker                          | 1968 Okamoto |
| Peppercorn                                  | Steamed meat dumpling maker                     | 1977 Okumura |
| Animal                                      | Silk                                            | 1966 Nakamura |
| Sea squirt                                  | Oyster farm worker                              | 1964 Jyo   |
| Alcyonarian                                 | Japanese spiny lobsterer                        | 1989 Onizuka |
| Animal hair                                 | Writing brush maker                             | 1968 Kikuchi |
| Mixed fertilizer (fish, crab)               | Fertilizer factory worker                       | 1982 Usami, 1991 Kaswagi |
| Sardine powder                              | Dried sardine factory worker                    | 1987 Takamoto |
| Baby chick feather                          | Hatchery worker                                 | 1971 Nemoto |
| Poultry manure                              | Poultry producer                                | 1972 Tateno |
| Coat of rat and guinea pig                  | Researcher                                      | 1972 Kobayashi |
| Pollen, spore                               | Sugar beet                                      | 1970 Matsuyama |
| Rose                                        | Researcher of sugar beet                        | 1978 Saito |
| Orchard grass                               | Commercial grower of orchard grass              | 1971 Nakazawa |
| Strawberry                                  | Worker in plastic greenhouses of strawberry     | 1973 Kobayashi |
| Peach                                       | Commercial grower of peach                      | 1973 shida  |
| Pear                                        | Commercial grower of pear                       | 1981 Tsukioka |
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of asthma associated with their work from around 1960. This asthma was reported at the annual congress of the Japanese Society of Allergology in 1963 by Mitsui et al. In addition, detailed studies revealed that this type of asthma was induced by the inhalation of sea squirt components adherent to oysters. Such OA was named sea squirt asthma in 1966 [9]. The cause of its onset was improved farming methods that allowed farming of oysters in deep water since around 1952, so that sea squirts became attached to the oysters. Because work was often done under rough conditions with poor ventilation, workers inhaled a lot of sea squirt components. The number of patients has recently shown a significant decrease due to improvement of the work environment.

From the investigation done at the time, the prevalence was 29% (443 out of 1,528 people) and it reached 45.8% in some towns. Because the industry mostly has female employees, there is a majority of female patients, but there is no gender difference in the prevalence. Half of the patients develop asthma within five years of starting work.

2) Antigen: Separation and purification of sea squirt antigen was carried out and four antigens (H, Gi-rep, Ei-M, DIIIa) were identified [9]. Gi-rep and Ei-M were effective when used for hyposensitization therapy. The epitope is a five sugar alcohol: as GalNAcα1→2Fucα1→3 (GalNAcβ1→4) GlcNAcβ→3GalNAc [10].

3) Specific antibody: The intradermal reaction to sea squirt antigen is positive in 91.3% of sea squirt asthma patients. When an antigen inhalation challenge test was done with sea squirt antigen, 4 out of 9 sea squirt asthma patients were positive.

4) Hyposensitization therapy: Initially hyposensitization therapy was done with the crude antigen and the efficacy rate was high at about 75%. However, hyposensitization therapy with the crude antigen caused side effects such as induction of asthma or urticaria. In contrast, therapy with the purified antigen has a higher efficacy rate of 91.5% and causes fewer side effects [9].

Characteristics of OA caused by chemicals

Since chemicals have a low molecular weight, they have no inherent antigenicity but become antigens by binding to human proteins. The main features of such asthma are as follows:

1) Exposure to high concentrations of chemicals may induce tissue damage and can cause bronchopneumonia.

Table 3. Continue

| Antigen         | Occupation                      | Reference   |
|-----------------|---------------------------------|-------------|
| Apple           | Artificial pollination worker   | 1978 Sawada |
| Cosmea          | Commercial grower of cosmea     | 1982 Inamizu|
| Insect flower   | Commercial grower of insect flower | 1974 Nakagawa |
| Grape           | Worker in plastic greenhouses   | 1984 Tsukioka |
| Pepper          | Worker in plastic greenhouses   | 1985 Okumura |
| Spore           | Shitake mushroom                | 1968 Kondo  |
| Club moss       | Worker in plastic greenhouses   | 1968 Kondo  |
| Smut fungus     | Dental technician               | 1969 Nakamura|
| Metal, chemical | Drug                            | Reference   |
| Diastase        | Pharmacist at drugstore         | 1970 Fueki  |
| Pancreatin      | Pharmacist at drugstore         | 1971 Nakamura|
| Semisynthetic penicillin | Pharmacist at drugstore     | 1974 Kanetani|
| Metal           | Dichromate                      | Industry worker | 1984 Shima |
| Chloroplatinate | workers of cement producing industry | 1972 Fueki |
| Chemical        | TDI, MDI                        | Polyurethane industry worker | 1970 Shima |
| Ethylenediamine | Plastic processing worker        | 1979 Nakazawa|
| Tetryl (explosive) | Painter                      | 1989 Inagaki|
| Acrylic resin emulsion | Painter              | 1990 Nakamura|

TDI, toluene diisocyanate; MDI, methylenediphenyldiisocyanate.
2) Because of their low molecular weight, chemicals also reach other organs and induce an immune reaction that causes extrapulmonary lesions.

3) In the case of industrial antigens, unlike those in fields such as agriculture, avoiding exposure by career change is relatively easy. It may be that the estimated number of patients is lower than the actual number.

4) Identification is difficult because specific IgE cannot be detected.

New occupational antigens

Some examples of new occupational antigens that have been found in Japan recently include imported materials and newly synthesized chemicals.

1) Among high molecular weight antigens, there have been reports of OA due to new types of imported wood. A furniture craftsman developed asthma and the results of inhalation challenge tests showed that the causative antigen of his asthma was the dust of Albiza Falcata (Falcata wood), which is a broad-leafed tree [11].

2) Among chemicals, there have been reports about occupational allergy induced by ortho-phthalaldehyde, which is used as a disinfectant solution for fiberscopes. Cases of ortho-phthalaldehyde-induced anaphylaxis began to be reported from around 2006. For example, anaphylaxis has been observed immediately after observation by a laryngeal fiberscope. Since various new chemicals will be developed in the future, we always need to pay attention to allergies caused by chemicals.

Diagnosis

We do not have guidelines or clear diagnostic criteria for OA and it is diagnosed at the discretion of each physician. Successful diagnosis of OA begins with suspicion and history taking is most important. Because control of symptoms has become easy due to progress with anti-asthma drugs, one problem is that doctors no longer make much effort to identify the causative antigen. The gold standard for diagnosis is an inhalation challenge test with the causative antigen, but such challenge tests are dangerous and can only be carried out in specialized hospitals. Thus, it is difficult to perform an inhalation challenge test for the definitive diagnosis of every patient in Japan. As an alternative, questionnaires are useful to detect OA. Although their sensitivity is as high as 80 to 90%, the specificity is low at 14 to 32% [1]. Recording daily peak flow is an extremely effective method of diagnosing OA. Measuring peak flow four times a day on holidays and working days combined with the recording of symptoms and drug use achieves a sensitivity of 73% and a specificity of 100% [12]. It is very important for symptoms to be more severe on the working day and lighter on long weekends and holidays.

When a suspicious substance is found, try to identify specific IgE by a skin reaction test or the RAST method. Identification of the causative antigen is difficult in the case of inorganic or low molecular weight antigens, because specific IgE cannot be detected.

Treatment

1) Avoidance of the causative antigen is most important. The incidence of allergic OA is greatly reduced by improving the work environment. Patients with konjac asthma in Gunma and sea squirt asthma in Hiroshima are rarely seen these days due to the development of environmental measures. When avoiding the causative agent is not possible, the physician should educate patients to reduce exposure by the use of protective equipment in the workplace. When workers are removed from their workplace to avoid exposure to antigens without economic support, they become impoverished and are unable to continue the treatment of their asthma. One third of patients with OA lose their jobs within six years of diagnosis in Western countries [13].

2) Drug therapy is the same as for the treatment of ordinary asthma.

3) Hyposensitization therapy is effective for patients who cannot change their job or have symptoms even after trying antigen avoidance and drug therapy. Our studies have shown that desensitization therapy with high molecular weight animal or plant antigens is very effective, and efficacy rate was 64.7%, 93.3%, 40.0%, and 91.5% for konjac asthma, sericulture asthma, flour asthma, and sea squirt asthma, respectively. However, desensitization to low molecular weight substances like chemicals and molds is not effective [3, 5].

Prognosis

It has been reported that deterioration of lung function due to continued exposure to an allergen is not prevented by drug therapy in patients with mild or moderate asthma [14]. Conversely, it has been reported that deterioration of lung function in mild or moderate asthma can be prevented by use of long-
acting β2-agonists and inhaled corticosteroids. Other important determinants of good recovery after cessation of exposure are normal lung function at the time of diagnosis and a short symptomatic period before avoidance of exposure [1]. However, we do not have definitive evidence about prognosis and this remains an area for future research in Japan.

Prevention

The allowable workplace concentrations of substances that are respiratory hazards have been determined based on the dose-response relationship in the general population. However, in patients with allergic OA, sensitization and the onset of symptoms is triggered by exposure to much lower levels than the allowable limit. Since the amount of exposure that causes sensitization varies greatly among individuals, the allowable concentration in the workplace cannot be set uniformly. Occurrence of OA is often treated as a personal matter, but how to determine the allowable levels of substances in the workplace is an issue for the future.

Guidelines for occupational allergic diseases in Japan

A guideline was released in Canada as long ago as 1998 [15], while the American Thoracic Society guidelines were published in 2005 [1]. In the same year, other guidelines were published in the United Kingdom that contained 52 statements and 22 recommendations based on evidence obtained from 223 papers [13]. These guidelines were revised in 2010. Other guidelines that described diagnosis and management in detail were published by The American College of Chest Physicians [16], while more guidelines were released in Spain (in 2006) and in Singapore (in 2008). These guidelines show wide recognition of the importance of OA.

On the other hand, there are no guidelines for the prevention, identification, and management of OA in Japan. A guideline for allergic diseases was released in 1993, but OA was not described in any of its 179 pages. Besides, in 2003, a guideline for prevention and management of asthma was published and it has been revised many times since then. However, even the latest edition only mentions OA in a few pages, and there are no detailed statements based on evidence as seen in Europe and America. Thus, the present state is delaying the establishment of measures for prevention, identification, and management, and also contributes to lack of social progress.

Problems related to OA in Japan

1. The Japanese Society of Allergology holds annual congresses, but symposiums on OA are not so frequent. They were held in Okayama in 1975, Maebashi in 1985, Nagasaki in 1990, Tokyo in 2003, Maebashi in 2004, and Tokyo in 2011. There is a lack of recognition regarding the importance of occupational allergy.
2. The work environment has improved in large enterprises under the direction of the government, but the smaller companies are not considered to have made enough effort in some cases.
3. Due to advances in medication, achieving control of symptoms medically tends to be emphasized and the search for causative antigens tends to be neglected. Thus, physicians often do not try to identify the causative antigen.

Action plan

1. Develop Japanese guidelines for the prevention and control of OA.
2. Develop a surveillance system to regularly check for OA among workers.
3. Build a system to share information about OA.
4. Share information on OA with other countries.
5. Provide education about OA to workers, employers, health care providers, and government agencies.

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