Vol.45, No.11 November 2002

JMAJ

Japan Medical Association Journal

CONTENTS

Outlook for Regional Health Care

JMAJ 45(11): 453–459, 2002

Komei ISHIKAWA

Vice-President, Japan Medical Association

Key words: Regional health care; Medical association; Clinic; Hospital

Introduction

Regional health care is an expression that is currently used without any incongruity; however, its meaning differs according to the person who uses it and it can signify anything from simply regional health care to a complete health care system in a particular region supported by clinics and hospitals.

The health care system is approaching a major turning point and a renewed reconsideration of how community health care is going to change, how it should change, is a task that I consider to be of significance to the health care of the nation.

Current Condition of Regional Health Care and Related Issues

1. The origins of regional health care

Beginning in 1965, social development was set forth as a national policy. To coincide with this, Dr. Taro Takemi, the former president of the Japan Medical Association (JMA) asserted that the aim of social development was the realization of improved social welfare for Japanese citizens in harmony with socioeconomic development, on the basis of the concept that health care is the application of medical science to society. To which end, and in recognition of the fundamental importance of adapting the philosophy that the main constituent of economic activities is the respect for humanity in regional settings, he convincingly elucidated the concept of regional health care as follows. "Development of the regional population from a health perspective is a field of the utmost importance and it is physicians and the activities of medical associations which are primarily responsible for conducting such developmental activities. Based on this line of thought, local medical associations instituted a regional health delivery system that was tailored to meet the particular characteristics of the regions. On the basis of these efforts and via the provision of appropriate health care, it would be possible to improve health in the regions. In other words, the maintenance and promotion of the health of the regional population is the desired aim of the system. This constitutes the ideology of so-called 'regional health care'."

At the heart of this concept of community health care lie transitions in the concept of health care itself. Formerly, it was normal practice for physicians to devote themselves to the care of patients, predominantly within health

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 9, 2001, pages 1173–1177).
The Japanese text is a transcript of a lecture originally aired on September 2, 2001, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

care facilities. However, the concept of health care has expanded in conjunction with advances in medical science and technology, leading to a common recognition by physicians and medical associations that comprehensive health care that includes convalescence after a failure in health, disease prevention and health promotion would contribute to improving health standards in the regions. This broadened the sphere of physicians' activities and simultaneously amplified their social mission.

In 1965, the establishment of organic links among hospitals and between hospitals and clinics was thought to be necessary to streamline and provide appropriate medical care. The opening of hospitals, the establishment and operation of medical association hospitals and the provision of clinical laboratory test facilities, were also considered desirable as a means of developing regional health care. Provision of appropriate medical care needed to be effectively implemented to develop various specialty hospitals, promote group activities, and the shared-use of facilities among hospitals and clinics in line with social objectives.

In the sphere of health care and public health activities, the medical associations advocated the appropriate utilization of a comprehensive health care system for regional health care and social welfare that encompassed medical care, disease prevention, rehabilitation, health education, mental health, maternal and child health, industrial health, health management (educational, occupational, among the general population). The medical associations postulated the need for consolidated activities since the inconsistent application of the various health care activities would be ineffective, and the need for guidance on and promotion of systematic activities by an independent body, i.e. medical associations.

As a matter of fact, the concept of comprehensive health care as proposed by JMA was finally guaranteed under law in a revision of the Medical Services Law enacted in 1992. Article 2.1 included the following statement on the philosophy of providing health care: "Health care upholds the principles of the respect for human life and the protection of dignity. It is implemented on the basis of relationships of trust between medical physicians, dental practitioners, pharmacists, nurses and other medical professionals responsible for providing health care, and the individuals receiving such care, and in response to the physical conditions of the individuals receiving such care. The content of health care should not merely comprise treatment but should also include high-quality and appropriate provisions to prevent the occurrence of disease and rehabilitation."

2. Current condition of regional health care

Based on this idea, local medical associations have continued to conduct various activities at medical association-operated hospitals, including the provision of medical care, vaccination, public health, maternal and child health, school health care, industrial health care, sports health care, and emergency/disaster medicine, centering on the shared-use of facilities, and additionally, to operate nursing training facilities, to the present day. However, not all facets have developed smoothly, and there is the perception that some of the activities in the sphere of regional health care have begun to deteriorate in quality

The following is a survey of the present status of the various regional health care activities.

(1) Industrial health care activities

With the aim of improving the nature of industrial health physicians and furthering their activities as one link in the provision of regional health care, JMA inaugurated a program to certify industrial health physicians in April 1990. According to the latest statistics, the number of industrial physicians certified by JMA has steadily increased and currently stands at 52,165. There are 347 regional industrial health centers nationwide, which aim to promote occupational health among the personnel of offices employing less than 50 staff that is not legally required to assign an industrial health physi-

cian. Prefectural and municipal authorities have established 42 industrial health care promotion centers to support the activities of industrial health physicians and the institutions involved in the provision of industrial health care, and local health association activities in this field are positively vigorous.

The ideology of applying industrial medicine to society advocated by former JMA President Takemi, which aims to promote overall health standards within the industrial system via the development of a system for industrial medicine and thereby to promote occupational health, formed the foundations of the current industrial health care system.

(2) Medical association shared-use facilities

Among medical association shared-use facilities, which originated with medical association hospitals and clinical laboratory test centers, there are currently 81 medical association hospitals, 42 medical examination centers, 86 compound medical examination/testing facilities, 527 facilities that include satellite home-visit stations, 99 home care support centers and 48 helper stations.

[Medical association operated hospitals]

In line with the legislation of medical-care programs enacted under the revision of the Medical Services Law in 1985, and in the same way as general hospitals, the majority of medical association operated hospitals in regions with a surplus of hospital beds were precluded from increasing the number of hospital beds or establishing new hospital facilities. At one point, there was even a decreasing trend in connection with the medical fee schedule. However, under the Medical Service Law, hospital beds at shared-use facilities were recognized as exceptional cases, and a tendency toward recovery in the number of hospital beds available became apparent as a result of the newly established regional medical care support hospital system enacted under the third revision to the Medical Services Law in 1997. In addition, the consolidation of national hospitals, together with the delegation of hospitals and entrusted hospital management has generated further increases in the number of hospital beds. Medical association operated hospitals epitomize the concept of shared-use and should be considered the origin of cooperative disease diagnosis, in that primary care physicians refer patients requiring in-patient treatment for admission, such patients subsequently undergo collaborative treatment provided by both their primary care physician and hospital physicians and are then returned to the supervision of their primary care physicians upon discharge. It is necessary to protect and cultivate medical association operated hospitals, which may form the base for regional health care.

[Regional medical care support hospitals]

Regional medical care support hospitals were systemized under the third revision of the Medical Services Law in 1997. These hospitals accept patients who are referred by their primary care physicians or by small and medium-size hospitals in the regions, and are designed to support regional health care. Accordingly, the most characteristic specifications (conditions) for the hospitals in question are as follows: the requirement to handle more than 80 percent patient referrals and the positioning of a steering committee with a representative from the local medical association in order to guarantee the support of primary care physicians in the region.

As of the present, August 2001, 33 hospitals have become regional medical care support hospitals, a figure which breakdowns into 26 association operated hospitals, 2 prefectural and municipal operated hospitals, 2 local authority operated hospitals, and 3 medical corporation operated hospitals. (Note: There were 35 regional medical support care hospitals as of October 1, 2001.)

Regional medical care support hospitals require public health care institution participation, and it is considered necessary for such hospitals to expand into all regions in order to promote health care delivery in local communities.

The previous health care delivery system

centered on public hospitals, however, private-sector hospitals and clinics are currently the main constituents of this delivery system in the regions. It is necessary to be cognizant of the fact that the mission/raison d'être of public health care facilities is to support the private-sector health care institutions that are the main providers of health care in the regions, and effect a change in mentality to reflect the transition to an era of private, as opposed to public, significance in the health care arena.

[Home visit stations]

The objective of the home visit stations established by JMA, is to provide home treatment to local residents (the patients) mainly by regional medical associations, and as such they differ from the stations attached to specific hospitals. Home visit stations epitomize the shared-use of facilities by physicians in the regions.

Long-term care insurance is applicable to home visit stations as medical association operated shared-use facilities, however, since the entry of profit-making enterprises has been authorized, it will be necessary to pay particular attention to how this affects such facilities in the future. Moreover, home visit stations are not independent entities, but are operated as part of a tripartite body including home care support centers and helper stations, and accordingly it is considered necessary to continue to provide support to those individuals in need of nursing care.

[Clinical laboratory test centers/ Medical examination centers]

Medical association operated clinical laboratory test centers have a long and illustrious history and have accumulated results over the years. However, since such centers are now in competition with the laboratory test centers run by profit-making companies and member physicians are selecting the low-priced facilities of the latter, medical association operated clinical laboratory test centers are facing an increasingly hard fight. In terms of attaching significance to the provision of a service to people, it is necessary to make efforts to streamline management by, for example, substantiating health management operations at centers for regional populations in line with the implementation of medical examination operations in order to improve health standards in the regions; target collaborative operation of clinical laboratory test centers; and to facilitate cooperation among neighboring centers so that they can be managed according to the characteristics of their individual fields.

Clinical laboratory test centers and medical examination centers are both regional health management centers and simultaneously, bases for providing information on health to local populations. In other words, it is necessary to confer the new function of health information centers. In addition, the use of medical association operated laboratory test centers is one link in the provision of regional health care and it is also necessary to alter the mentality of association members to this effect.

(3) Training centers for nurses, etc.

Of those nursing training center facilities established and managed by medical associations, JMA is heavily involved in the management of 26 three-year curriculum nursing training centers, 117 two-year curriculum facilities and 292 assistant nurse training centers.

The assistant nursing system was established in 1951, and medical associations have been particularly central to this type of training since the outset. The uniform cuts in financial assistance imposed under the so-called Fiscal Structural Reform Law of 1997, the decline in the population of young people under 18 years caused by the falling birth rate, the changes to be made in the curriculum for assistant nurses in 2002, under which the hours of training will be increased from 1,500 to 1,890 hours with the aim of improving the skills of such nurses, and the minimum requirement for full-time teachers to be increased from two to three, there has been a steady increase in the number of medical associations suspending such training. A total of 22 vocational nursing training centers suspended student recruiting in 2001.

The review of financial aid administration means that there can be no expectation of an increase in government subsidies in the foreseeable future. Although the sums involved were minimal, JMA was able to provide a fixed amount of financial assistance to assistant nurse training centers last year (2000), an expression of JMA's intention to improve the aptitude of assistant nurses and to promote the continued existence of this kind of system.

Nonetheless, the Shodoshima assistant nurse training center, which has a student quota of 15, is continuing to work hard despite difficult management conditions, due to the realization of the necessity for assistant nurses in regional communities. Given the need for assistant nurses in the provision of regional health care, the sustained promotion of their continued existence is necessary, even in the face of difficult managerial circumstances.

Against a background of a declining birthrate and an aging population, it is necessary to promote awareness of the importance of nursing and nursing care and the active participation in its provision whether it is among one or many people. In recent years, there has been an increase in the number of students enrolling in assistant nurse training courses not only among junior and high school graduates but also from among working members of society, which is evidence of the emergence of a new perspective on the assistant nurse system.

Recent Trends in Regional Health Care

The surge in the declining birthrate and the aging population has hastened the need for reforms of the social security system including the health care system, and it is currently difficult to forecast the recent trends surrounding regional health care.

With the aim of breaking the tight financial conditions and activating the economy, the government's Council on Economic and Fiscal Policy and the Council for Comprehensive Regulatory Reform, have made respective public announcements of "fundamental policies relating to economic and fiscal management and the structural reform of the economy and society," so-called muscular indicators, and "*interim* reports pertaining to six important fields."

These policies and the contents of the *interim* report are highly significant in the field of social security, and especially, in the field of health care.

The fundamental policies of the Council on Economic and Fiscal Policy were reported to the Prime Minister on June 21, 2001, and a cabinet decision was made on June 26th. Furthermore, the Council for Comprehensive Regulatory Reform released its *interim* report on July 24th.

One of the objectives of the Council on Economic and Fiscal Policy is to control the increases in total medical costs, while the Council for Comprehensive Regulatory Reform is striving for institutional reform. The content of the *interim* report released by the Council for Comprehensive Regulatory Reform contained the following specific policies in the field of health care; broadly, (1) public disclosure of health care information and the promotion of IT, (2) a review of the medical fee reimbursement system, (3) the reinforcement of the functions of insurers, and (4) the introduction of competition in the medical field while upholding efficiency. Dates have been set for the implementation of each of these measures.

In response to these measures, JMA has issued statements on both the fundamental policies of the Council on Economic and Fiscal Policy and the *interim* report of the Council for Comprehensive Regulatory Reform. It has also compiled a booklet for relevant parties and a pamphlet for the general public concerning its Structural Health Reform Plan. These have been widely distributed in a bid to gain understanding for the reforms being proposed by JMA.

JMA is strongly opposed to authorizing the

entry of private companies, which will induce the collapse of regional health care, and to authorizing hybrid health care, i.e. differences in the content of health care based on the gap between the rich and the poor.

If the entry of profit-making enterprises to the field of health care is permitted, quite naturally, medical corporations, which currently come under various regulations, will also have to be systematically revised and incorporated as joint-stock corporations or limited liability corporations. This will in turn result in the entry of large capital, and additionally, of foreign capital, bringing about the interlocking of medical facilities under the auspices of such capital, so that health care will become nothing more than one step in the profit-making activities of corporations. The result will be the culling of unprofitable departments, for example, health care in remote areas, emergency health care and pediatric health care. As might be expected, this will result in the disintegration of community health care, inclusive of school health activities and public hygiene activities.

The review and reform of the organizational structure of society as a whole must be instituted without exception; this is an essential task at the dawning of the 21st century. Should regional health care collapse, this will destroy the foundations of Japan's outstanding health care and will be a great misfortune to the people of this nation.

In Conclusion—the Future of Regional Health Care

In such ways, regional health care, which is on the verge of potential collapse due to internal factors such as the dimming awareness of health care in regional communities among members of the medical associations, and external factors such as the reforms from a financial standpoint, is approaching a crucial period in its history.

At this point and by way of conclusion, I would like to give some consideration to those areas that will need to be focused on if regional health is to be further developed.

In the first instance, in order for physicians and medical associations to protect the health of the population, a substantial reassessment of regional health care from its very beginnings is necessary to renew awareness of the significance of this branch of medicine.

Currently, health care is at a critical turning point; is it to be maintained for the common good or handed over to market mechanisms? If the principle of adhering to health care for common welfare is selected, then there is a need for reforms in perceptions and awareness. As physicians, each and every one of us needs to recall our reasons for choosing this profession and to once again consider how to conceive of and how to act in order to maintain and further develop regional health care for the population of this country.

I also consider that the revolutionary development in IT (information technology) will have a major impact on regional health care. While IT does connect to issues of the protection of personal information, in terms of the provision of health information to regional populations it can also be expected to produce new expansions in regional health care, by utilizing medical information on local communities accumulated and analyzed by medical associations, which has the potential to contribute to maintaining and improving health in the regions. JMA believes in the need to actively promote the provision of information on health care and medical practice and is accordingly in the process of setting up a website on the Internet to offer information on medical institutions to the Japanese public. Although digital patient records and medical fee receipts will rapidly gain popularity, I would like to request local medical associations to dedicate their activities to improving health standards for local communities in the regions by actively analyzing and providing information on regional health care.

In addition, declining birth rates and the

aging of the population are progressing ever more rapidly. However, while measures to address the aging population have been formulated within the field of regional health care, the formulation of countermeasures against falling birth rates has become an urgent task. In addressing this issue, it is not merely a question of enumerating individual measures on prenatal visits and emergency treatment for pediatric patients, or increasing child care facilities for convalescent pediatric patients or day-care centers. The construction of a child care support system to facilitate support from within society is important, as is elucidating the role to be played by local medical associations within such a system and the nature of the involvement of medical institutions. The prompt construction of this kind of child care support system will be a major pillar in regional health care, and is an important issue for this branch of health care in the future.

The construction of a child care support system and the socialization of child care are urgent tasks if we are to target the creation of a gender-free society in which both men and women can participate fully and a brighter future for the 21st century.

Diagnostic Standard for Atopic Dermatitis

JMAJ 45(11): 460–465, 2002

Joji TADA

Director, Division of Dermatology, Okayama Municipal Hospital

Abstract: For a dermatologist, the diagnosis of atopic dermatitis (AD) is relatively easy. In view of the fact that the increase and exacerbation of AD, confusion over its treatment and prevalence of abundant but not necessarily correct information are creating social issues in Japan, diagnosis and treatment of AD based on precise cognition are extremely important. While Hanifin and Rajka's diagnostic standard is known worldwide, a standard that is easily appreciated and handy for use by non-dermatologists is needed as many AD patients are being treated in departments of pediatrics, allergy, etc. In this context, the diagnostic standard established by the Japanese Dermatological Association is quite meaningful. By comparing the standard with other previously published diagnostic standards, this paper discusses in detail the main items of "pruritis", "exanthematous features and their distribution" and "chronically relapsing course", and emphasizes differential and exclusion diagnoses.

Key words: Atopic dermatitis; Diagnostic standard; Pruritis; Differential diagnosis

Introduction

Atopic dermatitis (AD) is diagnosed with relative ease based on its clinical symptoms regardless of sex or age of the patients. But not all the diagnoses are correctly rendered. The concept of AD proposed by Wise *et al.* (Table 1)[1] in 1933 has been accepted worldwide, and AD is now defined as "a disease mainly consisting of eczematous lesions with itch, following the course of exacerbations and remissions, and many of the patients have

Table 1 Concept of AD by Wise and Sulzberger[1]

(1)	Family history of atopic diseases
(2)	Preceded by infantile eczema
(3)	Localization to cubital and popliteal fossae, forehead, anterior thorax and face, particularly eyelids
(4)	Presence of gray to brownish skin
(5)	Absence of clinical and histological vesicles
(6)	Instability or easy irritability of vasomotor nerves
(7)	Patch tests with many irritating contact substances are usually negative
(8)	Instant positive wheal reaction against many scratch or intradermal tests
(9)	Presence of much serum regains

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 22–26).

Table 2 Definition and Diagnostic Criteria for Atopic Dermatitis by The Japanese Dermatological Association

Definition

Atopic dermatitis is a pruritic, eczematous dermatosis, the symptoms of which chronically fluctuate with remissions and relapses. Most individuals with atopic dermatitis have atopic diathesis.

Atopic diathesis: (1) Personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and atopic dermatitis), and/or (2) Predisposition to overproduction of immunoglobulin E (IgE) antibodies.

Diagnostic Criteria for Atopic Dermatitis

1. Pruritus
2. Typical morphology and distribution:
   (1) Eczematous dermatitis
   - Acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts
   - Chronic lesions: infiltrated erythema, lichenification, prurigo, scales, crusts

   (2) Distribution
   - Symmetrical
     Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk
   - Age-related characteristics
   * Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
   * Childhood phase: neck, the flexural surfaces of the arms and legs
   * Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest, and back)
3. Chronic or chronically relapsing course (usually coexistence of old and new lesions):
   * More than 2 months in infancy
   * More than 6 months in childhood, adolescence, and adulthood

Definite diagnosis of atopic dermatitis requires the presence of severity. Other cases should be evaluated on the basis of the clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.

Differential Diagnosis

- Contact dermatitis • Seborrheic dermatitis • Prurigo simplex • Scabies • Miliaria • Ichthyosis
- Xerotic eczema • Hand dermatitis (non-atopic)

Diagnostic Aids

- Family history (bronchial asthma, allergic rhinitis and/or conjunctivitis, atopic dermatitis)
- Complications (bronchial asthma, allergic rhinitis and/or conjunctivitis)
- Follicular papules (goose-skin)
- Elevated serum IgE level

Clinical Types (not applicable to the infantile phase)

- Flexural surface type • Extensor surface type • Dry form in childhood • Head · face · upper neck · upper chest · back type
- Prurigo type • Erythroderma type • Combination of various types are common

Significant Complications

- Ocular complication (cataracts and/or retinal detachment): especially in patients with severe facial lesions
- Kaposi's varicelliform eruption
- Molluscum contagiosum
- Impetigo contagiosa

atopic predisposition."[2] AD is, however, a complex inflammatory disease with Type I and IV allergies combined in a complicated manner, and not all the patients have atopic predispositions. In view of these points, it is necessary to recognize that AD is clearly different from other atopic diseases such as bronchial asthma and allergic rhinitis.

As the increase and exacerbation of AD, confusion over its treatments, and abundance of not necessarily correct information over AD are creating social problems today, the diagnosis and treatment based on precise cognition of AD is extremely important. As many AD

patients are being treated in non-dermatology departments such as pediatrics and allergy, a diagnostic criterion that is easily appreciated and handy for use by non-dermatologists is needed, and the significance of the diagnostic standard prepared by the Japanese Dermatological Association (Table 2)[2] is quite meaningful in this context.

Particular attention should be paid, however, to "diagnoses for exclusion" in the standard. Even after seven years since its publication, we often encounter patients with contact dermatitis caused by external preparations and non-drugs that have been prescribed for treatment purposes, or those whose AD has become exacerbated by non-drugs.[3] A physician unable to diagnose eczema lesions accurately by differentiating them as true AD lesion or complication of contact dermatitis is not qualified to diagnose AD.[4,5]

I would like to discuss the diagnostic standards of AD, its clinical features, and useful items for diagnosis.

Diagnostic Standards[4,5]

Several standards and guidelines for the diagnosis of AD have been published, all of which are substantially the same as the disease concept of AD published by Wise *et al.*[1] (Table 1). Rajika published the diagnostic standard of AD in 1961 for the first time in the world. Although it is somewhat insufficient from the contemporary standpoint, its historical significance is enormous.

In 1977, Hanifin *et al.* cited three essential features of (1) pruritis, (2) typical morphology and distribution of eruptions, and (3) chronic course of dermatitis. They further cited 13 features related to Type I allergy, physiological functions of the skin and complications, divided them roughly into two groups (four and nine), and proposed to diagnose AD when the patient meets two out of the four features of the former group or at least four out of nine of the latter group.

Table 3 Diagnostic Standard of Hanifin & Rajika[6]

1. Must have three or more basic features described below
   (1) Pruritus
   (2) Typical morphology and distribution
   Flexural lichenification in adults
   Facial and extensor eruptions in infants and children
   (3) Chronic or chronically relapsing dermatitis
   (4) Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

2. Must have three or more following minor features:
   (1) Xerosis
   (2) Ichthyosis/palmar hyperlinearity, keratosis pilaris
   (3) Immediate (type I) skin test reaction
   (4) Elevated serum IgE
   (5) Early age of onset
   (6) Tendency toward cutaneous infections (especially *staph. aureus* and *herpes simplex*), impaired cell-mediated immunity
   (7) Tendency toward non-specific hand or foot dermatitis
   (8) Nipple eczema
   (9) Cheilitis
   (10) Recurrent conjunctivitis
   (11) Dennie-Morgan infraorbital fold
   (12) Keratoconus
   (13) Anterior subcapsular cataracts
   (14) Orbital darkening
   (15) Facial pallor, facial erythema
   (16) Pityriasis alba
   (17) Anterior neck folds
   (18) Itch when sweating
   (19) Intolereance to wool ad lipid solvents
   (20) Periofollicular accentuation
   (21) Food intolerance
   (22) Course influenced by environmental and emotional factors
   (23) White dermographism, delayed blanch

In 1980, Hanifin and Rajka modified and combined their respective standards and proposed a new diagnostic standard (Table 3).[6] This standard cited the essential three features of Hanifin plus the individual or the family history of atopic disease as an essential feature, and proposed to diagnose AD when the patient meets at least three of these four items and also at least three of 23 minor features. This diagnostic standard is being relied on worldwide today, but many minor features are somewhat tedious. These minor features are being re-

examined currently, and we also reported the significance of infra-auricular fissures (fissures of the ear) in diagnosing AD.[7)]

Subsequently, the American Academy of Dermatology has published the diagnostic standard for AD, which is substantially the same as that of Hanifin & Rajika.[6)] Firm diagnosis of infantile AD is quite difficult and should be studied further. Seymour *et al.* reported a revised version of Hanifin & Rajika's standard[6)] for infants younger than 20 months old. The standard by the Japanese Dermatological Association[2)] notes that chronically relapsing course lasting at least two months as the basis for diagnosing infantile AD.

In Japan, the standards published so far include those of Masuda, of Hongou, of Uehara *et al.*, and more recently "Guideline for diagnosis of atopic dermatitis" of the Japanese Ministry of Health & Welfare (MHW).[4,5)]

The standard of Uehara *et al.* is quite concise as it cites (1) unique clinical picture and (2) chronic course repeating the seasonal cycle of exacerbations and remission, and is easy to understand by dermatologists who have precise cognition of clinical picture of AD. MHW's guidelines were prepared not necessarily for physicians only, have problems in the science of dermatology, and may mislead diagnoses of all eczema lesions in infants as AD.

The diagnostic standard for AD (Table 2) deliberated by the Academic Committee of the Japanese Dermatological Association[2)] cites (1) pruritis, (2) exanthematous features and their distribution, and (3) chronically relapsing course as the three features that should be manifested for diagnosing AD. The standard is concise and focuses on clinical symptoms of eruptions. Eight diseases such as contact dermatitis, seborrheic dermatitis, etc. are mentioned as those to be excluded in the diagnosis. Those physicians without adequate knowledge of diseases to be excluded may not be able to use the standard properly.

Items Important for Diagnosis

1. Pruritis

Pruritis is a symptom commonly seen in many cutaneous diseases, and there exists no AD without pruritis or traces of itch-induced scratching. Itchiness becomes intense toward night and often prevents sleep.

All of the diagnostic standards in which Hanifin and Rajika were involved[4–6)] and that of the Japanese Dermatological Association[2)] cite pruritis as the primary and essential feature. Although various causes are cited for pruritis in AD such as abnormality in cutaneous barrier function, increase in dermal mast cells, and increase of epidermal nerve ends, there remain many unclear points.

2. Features, distribution and course of exanthema

Dermatological symptoms of AD change with advance in age, and patients manifest uniquely different features according to their age. It is therefore essential to give full consideration to the age of the patient in diagnosis.

In infancy, exudative erythema, papules, exfoliative scales, and crusts are observed from the forehead, the cheeks to the front of ears accompanying traces of itch-induced scratching. Similar signs are observed from the forehead toward the parietal region, often accompanying adhesion of yellowish soft crusts. Eruptions are often observed also in the neck, trunk and limbs, but no exudation is observed except in the neck, cubital and popliteal fossae. At this period, differentiation from seborrheic dermatitis always presents a problem and diagnosis should be established after careful observation of the course.

In early childhood, exudative or erosive lesion decreases and xerosis increases. Lichenification appears in the cubital and popliteal fossae, nuchal region, shoulders, and hips, and because of intense itchiness, itch-induced scratch traces and crusts are apparent. Other features characteristic to this period include erythma with

lichenification in the forehead and infra-auricular fissures.[7)]

From pubescence to adulthood, lichenified erythema spreads from the cubital and popliteal fossae and neck to thoracodorsal region, upper limbs, lumbar and femoral regions. Compared to infancy, prurigo-like papules are more notable. As exanthema continues for long, it is often accompanied by complex and mixed phases of secondary thickening, pigmentation, and depigmentation. In adulthood, eruptions often appear at places other than the cubital and popliteal fossae where eruptions usually to appear. Recently, patients with relatively light eruptions in the trunk and limbs manifested severe eruptions in the face, neck, and upper thoracodorsal part.[3)]

While various signs characterize the respective age groups, there exist general and common findings of AD in all the groups that are easily recognized as such by any dermatologist. Eruptions in AD are mainly eczematous lesions, often accompanied by diffuse and symmetrical erythema. Another feature is that such exanthema takes a chronically relapsing course. These features are commonly described in the diagnostic standards for AD of the Japanese Dermatological Association and of Hanifin and Rajka,[2,6)] indicating that remissions by adequate treatment are followed by flare-ups. The important question is how to judge the degree of chronicity in infants and children. At any rate, it should always be remembered that AD subsides with advance in age if given adequate and proper treatment.[8)]

3. Laboratory tests

AD patients often manifest high total serum IgE, are positive against mite-specific IgE antibody, and experience peripheral blood eosinophil increase. It is reported that adult AD patients manifest a high positive ratio against *Pityrosporum*-specific IgE antibody, the incidence of *Staphylococcus aureus* detected from the diseased skin of AD patients is high, and the value of IgE antibody specific to the toxins produced thereby is also high.[9)] These matters related to type I allergy are not necessarily observed in all the AD patients. Although one cannot avoid diagnosing according to the standards focusing on clinical features, one should use these tests results as references only in order to avoid confusion in diagnosis since the disease entity of AD is already established.

The patients with higher than moderate degree of AD often manifest high serum LDH values, but they should be regarded as references to determine the degree of severity rather than for establishing diagnosis. Various intracutaneous tests for such as mites and foods are performed, but one should be aware that the results of food allergen tests do not necessarily correlate to RAST values while those of inhaled allergens do.

4. Differential diagnosis

Differentiating infantile AD and seborrhic dermatitis is quite difficult, and special care is taken in the diagnostic standard of the Japanese Dermatological Association. Although it may be necessary to consider the infancy separately from other periods as in the standards of Seymour *et al.*[4,5)] diagnoses during this period need to be established by careful observation of the course. Those patients who are subsequently diagnosed as AD tend to have lesions spread beyond the face and head from early days.

The standard of the Japanese Dermatological Association[2)] cites eight diseases such as contact dermatitis for differentiation, but others such as hyper IgE syndrome and Wiskott-Aldrich syndrome should also be differentiated. There are quite a few patients who develop contact dermatitis by external preparations prescribed for AD and whose dermatitis is being overlooked.[3)] Special care should be taken in this regard.

Conclusion

Diagnosis of AD should be made by refer-

ring to adequate diagnostic standards as well as by taking detailed history (the age at onset, clinical course, histories of treatment, family, past diseases, and occupations, living environment, life style, etc.). Diagnosing AD may be described as diagnosis by exclusion, and differential diagnosis is, as discussed above, very important. By being aware that factors for exacerbation differ from patient to patient in AD, one should take meticulous care in treating them.

REFERENCES

1) Wise, F. and Sulzberger, M.B.: Editorial remarks, In *The 1933 Year Book of Dermatology and Syphilology.* Year Book Publishers Inc., Chicago, 1933; 59.
2) The Japanese Dermatological Association: Japanese Dermatological Association Criteria for the diagnosis of atopic dermatitis. *J Dermatol (Tokyo)* 1996; 23: 66–67.
3) Tada, J., Yamasaki, H., Toi, Y. *et al.*: Is the face and neck pattern of atopic dermatitis in Japan a special variant? *Am J Contact Dermatitis* 1999; 10: 7–11.
4) Tada, J. and Arata, J.: Diagnosis of atopic dermatitis. *MB Derma* 1997; 1: 1–7. (in Japanese)
5) Arata, J. and Tada, J.: Diagnostic standard for atopic dermatitis. Nishioka, K. ed. Atopic Dermatitis Morbidity and Treatment, revised edition, Iyaku Journal Sha, Tokyo, 1997; pp. 13–15. (in Japanese)
6) Hanifin, J.M. and Rajka, G.: Diagnostic features of atopic dermatitis. A*cta Derm Venereol Suppl (Stockh)* 1980; 92: 44–47.
7) Tada, J., Toi, Y., Akiyama, H. *et al.*: Infra-auricular fissures in atopic dermatitis. *Acta Derm Venereol* 1994; 74: 129–131.
8) Kawashima, S., Takigawa, M., Nakagawa, H. *et al.*; Japanese Dermatological Association ed. "Guideline for treating atopic dermatitis". *Jap J Dermatol* 2000; 110: 1099–1104. (in Japanese)
9) Morishita, Y., Tada, J., Sato, A. *et al.*: Possible influences of *Staphylococcus aureus* on atopic dermatitis — The colonizing features and the effects of staphylococcal enterotoxins. *Clin Exp Allergy* 1999; 29: 1110–1117.

Advisory Guidelines for the Avoidance of Exacerbating Factors of Atopic Dermatitis in Daily-Life

JMAJ 45(11): 466–471, 2002

Ichiro KATAYAMA*, Motoi TAKENAKA** and Kenshi YAMAMOTO***

Professor, Lecturer**, and Senior Lecturer***,*
Department of Dermatology, Nagasaki University School of Medicine

Abstract: This article describes current information on factors exacerbating atopic dermatitis (AD) and guidelines for daily-life routines that may be adopted to avoid such exacerbating factors. The prevalence of atopic dermatitis and its refractoriness to treatment have now become matters of public concern. This phenomenon may be explained by multiple factors, such as increase in the prevalence of the responsible allergens attributable to changes in housing conditions, weakening of the skin barrier resulting from alterations of life-style and obsession with cleanliness, inappropriate use of steroid ointments, a flood of folklore medicines, and emotional factors, including stress. To cope with refractory AD, the exacerbating factors should first be identified in individual cases. A partnership between the patient and physician is of great importance in precluding the identified exacerbating factors from the living environment. It is essential in the treatment of AD, to focus on daily-life guidance to eliminate exacerbating factors, adapted for each patient, combined with a skin care routine, appropriate use of topical steroid preparations based on patient education, and drug therapy for pruritus control.

Key words: Atopic dermatitis; Skin barrier function; Exacerbating factors; Daily-life guidance

Introduction

The prevalence of atopic dermatitis (AD) and its refractoriness to treatment have now become matters of public concern. An upsurge of AD in adults since 1980, alterations in the disease pattern of AD, and an increasing number of severe cases with refractory AD have often been pointed out.[1)] Although the cause of the increase in number of adults with AD and severe AD remains unclear, increase in the prevalence in the environment of the respon-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 37–40).

Table 1 Changes in Hypotheses over the Years for the Etiology of Atopic Dermatitis

1892	Atopic dermatitis was first described as a genetic, constitutional disease by Pruigo Besnier
1933	Atopic allergy hypothesis
1958	Disrupted skin function disorder (white dermographism)
1968	β-receptor disorder (enhanced epidermal hyperplasia)
1981	Contact dermatitis due to human dander
1982	Late phase reaction induced by IgE antibody
1989	Dust-mite-reactive Th2 lymphocytes/cytokines
1989	IgE-FcεR1 gene polymorphism
1993	Impaired skin barrier function
1993	Superantigen produced by *Staphylococcus aureus*
1996	Decreased reactivity to tuberculin
1997	IL4 receptor gene polymorphism
1998	Autoimmune disease by self-antigen

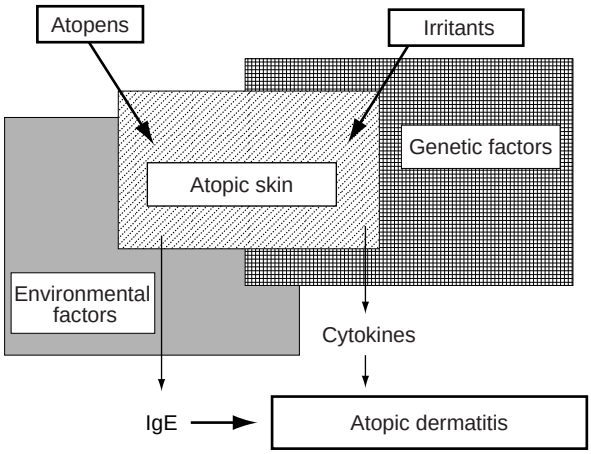


Fig. 1 Assumed biphasic pathogenesis of atopic dermatitis—atopens and irritants

sible allergens, attributable to housing conditions, weakening of the skin barrier function resulting from alterations of life-style, inappropriate use of steroid ointments, and a flood of folklore medicines have been proposed.[2)]

A sharp rise in the prevalence of AD has generated widespread concern in Japan. The Japanese Dermatological Association has developed diagnostic criteria for AD,[3)] a scoring system to determine the severity, and guidelines for the treatment of AD.[4)] A national epidemiological study on AD has also been initiated by the Ministry of Health, Labor and Welfare. These efforts may be rewarded by the establishment of more effective treatment modalities for AD and better patient education, directed at radical therapy of the allergic disease. From these standpoints, careful treatment of AD and daily-life guidance should be provided in clinical practice to the patients after identification of the exacerbating factors in individual patients.

Pathogenesis of Atopic Dermatitis

Since it was first proposed by Besnier *et al.* that AD was a familial or constitutional skin disease, many different hypotheses on the etiology of AD have been published, reflecting the new scientific dogma and discovery of the day (Table 1). Dermatologically, physiological disorders, such as skin and airway hypersensitivity, are considered to greatly influence the

development and progression of AD in people with an inherited allergic disease trait, characterized by overproduction of immunoglobulin E (IgE).

As shown in Fig. 1, the skin of a patient with AD is often very susceptible to allergy and is called atopic skin. Such vulnerability of the skin may result from a combination of genetic and environmental factors. Environmental allergens involved in atopic disease, such as house dust mites, referred to as atopens, trigger the overproduction of IgE antibody when they come in contact with sensitive, atopic skin, while irritants induce epidermal keratinocytes and fibroblasts to release various types of cytokines and predispose to skin inflammation. External skin preparations, cosmetics, and shampoos can also cause allergic contact dermatitis in some people.

Thus, when we review the pathogenesis of AD in terms of atopens and irritants, factors further triggering the already overactive immune system producing IgE antibody should be analyzed in allergic inflammation. At the same time, a detailed investigation of non-allergic factors impairing the physiological functions in the skin is required.[5–6] Inappropriate treatment of AD mentioned above also needs reviewing.

No national epidemiological study on the cause of AD has been conducted in Japan. There are several conceivable reasons. Firstly, no diagnostic criteria have been clearly established for AD in Japan until 1994.[3] Secondly, data integration is difficult, since medical treatment of AD is conducted at several departments of a hospital, including the departments of dermatology, pediatrics, and internal medicine. Furthermore, the disposition of the patient population seen from university hospitals to local clinics varies. At present, we have to speculate the epidemiology of AD in our country from the results of small-scale surveys.

A recent study by Ueda *et al.* demonstrated that the morbidity rate of allergic diseases, including AD, in children aged 3 to 15 years who underwent medical checkups in Aichi prefecture, was 132/1,512 (8.7%) in city areas, 52/983 (5.3%) in suburban areas, and 46/994 (4.6%) in rural areas, the variations in the rate among the different areas being statistically significant.[7] Factors involved in the increase in AD morbidity rate in city inhabitants and adults are complex. The results of a thorough epidemiological study on AD are awaited.

Living Environment and Atopic Dermatitis

In examining how the living environment influences the development, progression, and refractoriness of AD in each patient, the following considerations may be necessary:

1. Factors contributing to overproduction of IgE antibodies

Ever since the suggestion by Sulzberger that AD might be associated with the overproduction of IgE antibodies, IgE has been considered to play an important role in the pathogenesis of AD. However, the details of the involvement of IgE antibodies in the onset of AD remain unknown. Clinical observations have revealed elevation of IgE levels in aggravated AD and elevated IgE titers in proportion to the disease duration in AD. Experimental studies have shown that FcεR1 (+) Langerhans cells in the skin of patients of AD are more active in presenting antigens inducing the production of IgE to T cells. These findings indicate that IgE contributes to the development and progression of AD in many ways.

Airborne allergens, such as house dust mites, molds, pollens, and animal dander, food allergens, microorganisms, metals, and chemicals are commonly known to induce AD. Immunological studies have indicated that the allergens might more strongly induce the proliferation of Type 2 helper T cell (Th2), which stimulates the production of IgE. Frequent exposure to allergens in the living environment leads to overproduction of IgE.

An increase in the prevalence of house dust mites and molds among these allergens could

be attributed to insufficient natural ventilation due to the adoption of air sealing, aluminum-mesh doors/windows, and carpeting, which have rapidly become popular since the 1960's. Hot humid air emitted from open-type heaters, including oil heaters, also contributes to allergen-filled indoor environments. Condominiums and pre-fabricated houses are the clearest examples of air-sealing and heat insulation.[8)]

Besides, carpets, curtains, sofas, beds, pillows, and stuffed toys that are rarely washed and left around in rooms are good places to find mites. Widespread use of air conditioners, cooking and washing in ill-ventilated homes, and indoor cultivation of tropical fish and foliage also provide favorable environments for the propagation of mites and molds. Pet animals themselves, including dogs and cats, can be a source of allergens, when they are reared indoors. Therefore, patient education is important for the avoidance of these allergens.

Screening tests for atopy conducted yearly on new students at Nagasaki University reveals that the AD morbidity rate is 7 to 8%, while the positivity rate for IgE antibodies specific to dust mites, cedar pollen, and other allergens has been increasing, now at 50%. Metal allergy attributable to the use of various kinds of metal ornaments, and drug allergy owing to the overuse of antibiotics are also evident.

Concerning pollens, Japanese cedar pollen has always drawn much attention as a source of allergens in our country. In fact, dermatitis in the face and other body sites periodically flare up in a significant number of Japanese people during the months of February and March every year. Many of these people have allergy to Japanese cedar pollen. Skin scratch and patch tests also support the contention that cedar pollen triggers the flare of dermatitis in these patients. However, pine pollen and ragweed pollen, which may also be the cause of atopic dermatitis, should not be ignored.

Although food allergy occurs in a limited number of cases of adult AD, proper monitoring is required if redness of the skin or other skin symptoms appear in infants and children after food intake. Parasitic infections, once common in children, are now rarely seen in Japan. The number of patients with tuberculosis has dropped greatly. With this background in mind, some researchers have proposed that a Th1 to Th2 shift in the immune response may be responsible for the increased morbidity rate of AD.

2. Impairment of physiological functions of the skin

Various types of skin dysfunction are observed in patients with AD. Recent studies have indicated that a impaired skin barrier function might be responsible for the skin to become dry and more vulnerable to such allergens as microorganisms and mites. The skin barrier function is conditioned by ceramide, a major component of corneous interstitial cell lipids, and natural moisturizing factor (NMF), which helps to keep the skin moist. There are also sweat-derived molecules involved in pH control and elimination of microorganisms, secretory IgA, and cytokines, including IL-1, in the skin. Abnormal production of these factors may lead to disruption of integrity of the skin barrier.[9)]

Daily morning shampooing, which has become a phenomenon among senior high school students, can exacerbate dermatitis in the face and hands.[10)] Since most houses now have a bathroom, daily baths are commonplace; daily baths can damage the natural skin barrier and worsen dermatitis. Further studies are required to clarify the involvement of these factors in AD.

The relationship between air pollution and AD has not been investigated in pilot studies, as in the case of asthma and rhinitis. The effect of nitric oxide and sulfides on the skin has been discussed in several studies. Ultraviolet rays have been reported to exacerbate AD in some cases.

3. Treating atopic dermatitis

In the past few years, impaired development in children resulting from strict food restriction, skin disorders attributable to the indiscrimi-

nate use of corticosteroid ointments, and the flood of folklore medicines for the skin with no scientifically proven efficacy have become problems in the treatment of AD in daily practice.

The harm done by extensive food restriction has already been clarified. Eliminating a proven allergenic food or desensitization by using minimal quantities of the food-borne allergens in the food may prove effective in the control of AD.

The use of topical steroid preparations is often beneficial if they are used according to the directions prescribed in the guidelines developed by the Japanese Dermatological Association. Abrupt cessation of steroid therapy or switch to other therapy without physician supervision, influenced by the propaganda in mass media, folklore medicines, or word of the mouth, have resulted in of great importance in the management of AD. It is therefore important to establish a good relationship between the patients and the physicians in the treatment of AD.

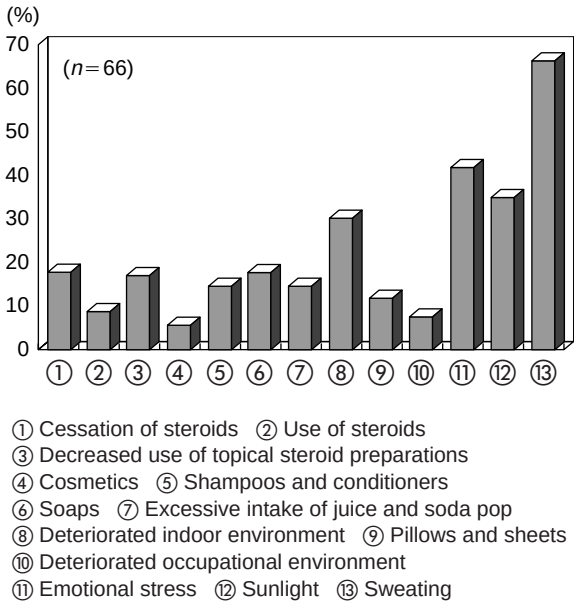


Fig 2 Factors causing exacerbation of atopic dermatitis as determined from our questionnaire survey of patients with AD

Factors causing Exacerbation of AD

To identify factors causing exacerbation of AD in individual cases in order to guide the treatment, we usually deliver a questionnaire to our patients. As is evident from the responses to the questionnaire shown in Fig. 2, many subjects believe that sweating, emotional stress, sunlight, and a deteriorated housing environment are exacerbating factors. The use of soaps and shampoos are reported to be detrimental in some patients. Since multiple exacerbating factors are found in some severe cases of AD, it is essential to make the effort to identify these factors and eliminate them from the environment for each patient, through taking a proper detailed medical history or other appropriate means.

Conclusion

It is essential in the treatment of AD, to focus on daily-life guidance to eliminate exacerbating factors, adapted for each patient, combined with a skin care routine, appropriate use of topical steroid preparations based on patient education, and drug therapy for pruritus control.

REFERENCES

1) Katayama, I.: Allergic dermatitis and its prolongation. *Immunopharmacology & Therapy* 1994; 12: 57–64. (in Japanese)
2) Katayama, I.: Modern life and atopic dermatitis. *Popular Medicine* 1996; 186: 32–37. (in Japanese)
3) Japanese Dermatological Association: Diagnostic criteria for atopic dermatitis. *The Japanese Journal of Dermatology* 1994; 104: 1210. (in Japanese)
4) Japanese Dermatological Association: Treatment guidelines for atopic dermatitis. *The Japanese Journal of Dermatology* 2000; 110: 1099–1104. (in Japanese)
5) Katayama, I.: Keywords for atopic dermatitis and their interpretation (1) IgE antibody and atopic dermatitis. *The Nishinihon Journal of Dermatology* 1998; 60: 515–519. (in Japanese)

6) Katayama, I.: Etiology and pathogens of adult type atopic dermatitis. *MB Derma* 2000; 31: 9–15. (in Japanese)
7) Ueda, H.: *Comprehensive Research Report for Allergic Disease*, Ministry of Health and Welfare. 1993; pp. 296–300. (in Japanese)
8) Bougaki, K.: *Comprehensive Research Report for Allergic Disease*, Ministry of Health and Welfare. 1993; pp. 54–56. (in Japanese)
9) Matsunaga, T., Katayama, I., Yokozeki, H. *et al.:* ICAM-1 expression on keratinocytes in mechanically-injured skin of a patient with atopic dermatitis. *J Dermatol Sci* 1996; 12: 219.
10) Taniguchi, Y., Yokozeki, H., Ohki, M. *et al.*: Patch test for the elimination of exacerbating factors of AD in severe cases. *The Japanese Journal of Dermatology* 1997; 107: 781–785. (in Japanese)

Guidelines for Care of Atopic Dermatitis 2001

JMAJ 45(11): 472–476, 2002

Osamu KORO

Chief, Division of Dermatology, Hiroshima Prefectural Hospital

Abstract: Since the etiology of atopic dermatitis has not been fully elucidated, no fundamental treatment based on its cause is available. In addition, the facts that the disease is intractable, that there is anxiety about adverse reactions to topical steroid therapy, as well as that there are many folk remedies have created confusion in the care of atopic dermatitis. These guidelines have been prepared for the purpose of describing strategies to deal with this situation. In this paper we report on the "Guidelines for care of atopic dermatitis 2001."

Key words: Atopic dermatitis; Treatment guidelines

Introduction

There is currently no fundamental etiology-based treatment for atopic dermatitis (AD), and the conventional treatment has consisted of symptomatic drug therapy with oral antihistamines and topical steroids. However, since AD is generally intractable and there is anxiety about the adverse effects of topical steroids, numerous methods of treating AD have been proposed, including a wide variety of folk medicine treatments, and the emergence of patients who refuse the use of topical steroids, etc., have created confusion regarding treatment, not just in medical settings but among the general public.

In light of this situation, the Ministry of Health and Welfare Long-term Chronic Disease Comprehensive Research Project, Allergy Comprehensive Research, Atopic Dermatitis Study Group began preparing treatment guidelines for AD in 1996, and it was continued in 1997 in the form of Health Science Research[1–4] supported by the Ministry of Health and Welfare.

In this paper we describe the "Guidelines for care of atopic dermatitis 2001," which were revised and published in 2001 on the basis of research achievements up until that time.

Method of Preparing the Guidelines

The guidelines were prepared as a result of discussions by the research collaborators whose names are listed at the end of the guidelines. The first guidelines "Guidelines for care of atopic dermatitis 1999" were issued on the basis of research achievements up until that time. A questionnaire survey on the contents of the guidelines 1999 was conducted among dermatologists (400 members of the Japanese Society of Dermatoallergology), pediatricians (400 members of the Japanese Society of Pedi-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 41–44).

atric Allergy & Clinical Immunology), and internists (200 from the "Membership List of the Patient-supporting Medical Specialists" edited by the Japanese Allergy Foundation, all selected randomly) and the results were used for reference in revising them.

Contents of the Guidelines

1. Reason for preparing the guidelines and their targets

The preface to the guidelines states that the reason for drafting them was "to outline the care of atopic dermatitis, which sometimes tends to be confusing." It also states that the guidelines are designed for clinicians who are involved in the care of AD, that clinicians other than specialist are also included.

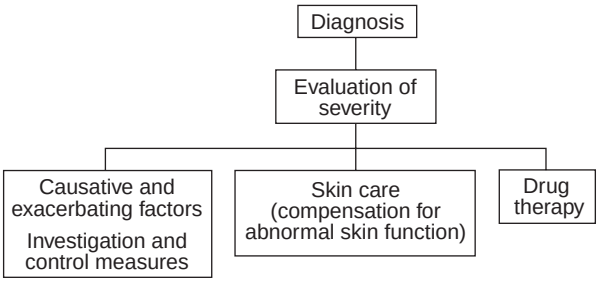


Fig. 1 Outline of the treatment guidelines

2. Concept of AD and main points of the guidelines (Fig. 1)

Next, the main points of the guidelines are described. The guidelines say that the first step in the course of care is to make the diagnosis, then properly evaluate the severity of AD, and finally administer treatment. The foundation of treatment is 1) investigation and control of causative factors and exacerbating factors, 2) skin care, and 3) drug therapy. In the past, drug therapy was used first, but for patients who did not respond well to the drug therapy, causative factors were investigated and therapeutic measures were carried out. An integrated approach based on these three methods is the basic treatment recommended in the guidelines.

3. Diagnostic criteria

"Definition and Diagnostic Criteria for Atopic Dermatitis" (Japanese Dermatological Association)[5] and "Diagnostic Manual for Atopic Dermatitis" (Ministry of Health and Welfare)[6] are currently available as widely known references for diagnostic criteria. Their contents are essentially the same, and they have been evaluated as consistent when used as diagnostic criteria.

4. Standards for evaluating severity (Table 1)

Since no evaluations of the severity of AD

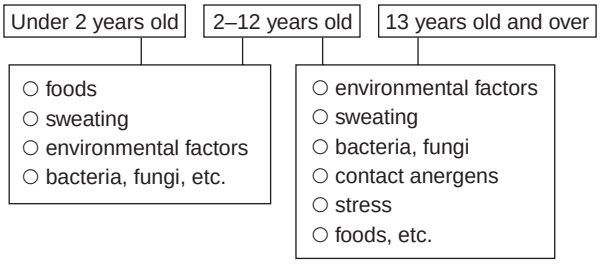
Table 1 Standards for Evaluating Severity

Several criteria have been proposed for evaluation of the severity of atopic dermatitis, but because expertise is required to use them, the new and simple degrees of severity listed below have been established to use as standards for purposes of treatment.	
Mild:	Only a mild rash*, regardless of its extent is seen.
Moderate:	A rash** associated with severe inflammation is seen over less than 10% of the body surface.
Severe:	A rash** associated with severe inflammation is seen over more than 10% but less than 30% of the body surface.
Very severe:	A rash** associated with severe inflammation is seen over 30% or more of the body surface.

*Mild rash: Lesions mainly consisting of mild erythema, dryness, and desquamation.

**Rashes associated with severe inflammation: Lesions associated with erythema, papules, erosion, induration, lichenification, etc.

have been universally verified, for the sake of convenience the guidelines provide a rough standard by classifying them into "mild," "moderate," "severe," and "very severe." It makes evaluation convenient by allowing severity to be evaluated according to the area of the body surface occupied by "the skin lesion associated with severe inflammation," and it provides clinical photographs of representative "mild skin lesions" and "skin lesions associated with severe inflammation" for reference in making evaluations.



Note: Since causative and exacerbating factors differ from patient to patient, eliminate them only after confirming their involvement in each individual patient.

Fig. 2 Causative and exacerbating factors

5. Causative and exacerbating factors (Fig. 2)

The exacerbating factors of AD are well known to be diverse, and for that reason the causative and exacerbating factors mentioned in the guidelines are only representative. They comment that since the actual frequency of involvement of causative and exacerbating factors has never been accurately assessed, examination of them requires detailed clinical observation and testing in each case. We also wish to emphasize that the basic principle is to eliminate exacerbating factors only after their involvement has been confirmed. "Sweat" has been added to the 2001 edition as a new exacerbating factor.

6. Skin care (Table 2)

We defined "skin care" as compensation for abnormal skin function, and the guidelines explain that the abnormal skin functions in AD are 1) decreased ability to retain water in the stratum corneum, 2) decreased threshold of itch, and 3) susceptibility to infection. Table 2 lists specific methods of skin care. The methods listed in the guidelines are representative, and

Table 2 Skin Care (Compensation for Abnormal Skin Function)

1. Skin cleanliness Bathe or shower every day • Remove sweat and dirt promptly. But don't rub hard. • Avoid soaps and shampoos with powerful detergency. • Rinse sufficiently so that no soap or shampoo remains. • Avoid water that is so hot that it causes itchiness. • Avoid bath agents that cause a flushing sensation after bathing. • Instruct the patient or guardian how to wash in accordance with the patient's skin condition. • After bathing, apply an appropriate topical agent, as needed.
2. Keeping the skin moist Emollients • Use emollients to prevent dry skin. • Apply emollients as needed after bathes or showers. • Select an emollient that the individual patient prefers to use. • Mild dermatitis sometimes improves in response to emollients alone.
3. Others • Keep indoor areas clean, maintain them at a suitable temperature and humidity. • Wash new underwear before wearing. • Use detergent with a low surface-active agent content. • Cut nails short, and scratch as little as possible.

Table 3 Basics of Drug Therapy

1. Select the potency, the dosage and the vehicle of the topical steroid according to the site, properties of the individual rashes and age of the individual patients, in addition to the severity of the disease.
2. Keep the following points in mind when using topical steroids:
   1) When topical steroids are used on the face, use the weakest steroid possible for only a brief period.
   2) Since rashes sometimes suddenly worsen when topical steroids are abruptly discontinued after protracted use, advise the patient to follow the physician's instructions regarding discontinuation and changes.
   3) Routinely monitoring the potency and dosage used is recommended.
3. Depending on the severity of the manifestations, use suitable topical preparations that do not contain steroids.
4. Use oral antihistamines as needed.
5. Evaluate the severity of disease every 1 or 2 weeks as the standard interval, and consider switching to another drug.

they have been summarized as 1) methods related to the cleanliness of the skin, 2) methods related to emollients, and 3) methods related to nonspecific external irritation. At the end of the 2001 edition there is a chart listing emollients.

7. Basics of drug therapy (Table 3)

At present, when the basic mechanism of AD is still unknown, there is no choice but to select treatments that are commonly used by many physicians responsible for the clinical care of AD patients. Topical steroids and oral antihistamines are currently recognized as the major treatments. Taking the absorption of topical agents according to age into consideration, the guidelines list the drug choices by age. In terms of practical application, the guidelines say to evaluate severity of the lesions at the intervals of one to two weeks, then switch to another topical steroid when necessary, say to avoid application of topical steroids to the face as far as possible, and recommend an inpatient treatment is desirable in the very severe cases. The 2001 edition adds a caution against sudden steroid withdrawal to prevent severe recurrence of inflammation, and it recommends steroid dose monitoring routine to prevent adverse effects of topical steroids.

8. Precautions during the course of treatment

Several items that require caution in regard to the care of AD patients are mentioned. One concerns the variety of infections that occur against the AD's background of susceptibility to infection, and the next is in regard to occular complications. The possibility of traumatic factors being linked to cataracta and retinal detachment in the eye are pointed out in particular.

Conclusion

The guidelines are characterized by a focus on topical steroids as drug therapy. However, because of their adverse effects, the use of some topical steroids for the treatment of AD is still controversial. The results of a questionnaire survey regarding the guidelines showed that no one thought that topical steroids should be completely ruled out as a treatment for AD, however, needless to say, neither their easy use or rejection for no reason are beneficial to the patients. Objective data on the use of topical steroids should be obtained, and a survey on topical dosage and adverse reactions is being conducted by Health Sciences Research.[7,8] The results should serve as a basis for further improvements to the guidelines.

REFERENCES

1) 1996 Comprehensive Research Project on Chronic Disease, Allergy Comprehensive Research Report, Ministry of Health and Welfare: Preparation of diagnostic criteria and guidelines (draft) for care of atopic dermatitis. 1997; pp. 125–130. (in Japanese)
2) 1997 Grants for Health Science Research: Research Project on Immunity and Allergy (Immunity/Allergy Section) Research Report, Ministry of Health and Welfare: Preparation of guidelines (tentative draft) for care of atopic dermatitis. 1998; pp. 25–29. (in Japanese)
3) 1998 Grants for Health Science Research: Research Project on Immunity and Allergy (Immunity/Allergy Section) Research Report, Ministry of Health and Welfare: Establishment and evaluation of guidelines for care of atopic dermatitis. 1999; pp. 113–117. (in Japanese)
4) 1999 Grants for Health Science Research: Research Project on Immunity and Allergy (Immunity/Allergy Section) Research Report, Ministry of Health and Welfare: Research related to the preparation and evaluation of guidelines for care of atopic dermatitis. 2000; pp. 108–110. (in Japanese)
5) Japanese Dermatological Association: Definition and diagnostic criteria for atopic dermatitis. *Nippon Hifuka Gakkai Zasshi* 1994; 104: 1210. (in Japanese)
6) Ministry of Health and Welfare, Children and Families Bureau, Maternal and Child Health Division (editorial supervision): *Handbook for Living with Atopic Dermatitis*. Nankodo, Tokyo, 1994; p. 54. (in Japanese)
7) 1998 Grants for Health Science Research: Research Project on Immunity and Allergy (Immunity/Allergy Section) Research Report, Ministry of Health and Welfare: Research on topical steroid dosage for atopic dermatitis. 1999; pp. 110–112. (in Japanese)
8) 1999 Grants for Health Science Research: Research Project on Immunity and Allergy (Immunity/Allergy Section) Research Report, Ministry of Health and Welfare: Research on topical steroid dosage for atopic dermatitis. 2000; pp. 111–113. (in Japanese)

Treatment of Atopic Dermatitis with Immunomodulatory Drugs

JMAJ 45(11): 477–482, 2002

Hidemi NAKAGAWA

Professor, Department of Dermatology, Jichi Medical School

Abstract: Atopic dermatitis is a common, intensely pruritic, chronic inflammatory skin disease that significantly affects the patients' health and quality of life. Major standard treatments directed at controlling the predominant symptoms of atopic dermatitis, namely, eczematous lesions and pruritus, include topical steroids and antihistamines. However, there are several concerns in regard to the treatment with topical steroids, especially when used long term or on the face and neck. Topical immunomodulators such as tacrolimus ointment represent a new therapeutic option specifically developed for the treatment of atopic dermatitis without the unwanted local side-effects of topical steroids. Systemic immunomodulators such as cyclosporin represent a new therapeutic option developed specifically for the treatment of severe refractory atopic dermatitis resistant to conventional therapies. This article reviews the future role of these immunomodulators in the treatment of atopic dermatitis.

Key words: Atopic dermatitis; Topical steroid; Tacrolimus ointment; Cyclosporin

Introduction

In general, the treatment of atopic dermatitis (AD) can be roughly categorized into treatment (remission) of existent cutaneous inflammation (eczematous lesions) and prevention of new inflammation. It is important to achieve rapid remission of inflammation; when the inflammation is prolonged, skin lesions such as lichenification and prurigo may develop, which are resistant to treatment. In the cutaneous inflammation associated with AD, not only activated T cells (Th2 and Th1), but also other inflammatory cells, such as mast cells, Langerhans cells, and eosinophils are known to be involved in a complex manner. Drugs that inhibit all of these cells could therefore be expected to exhibit prompt therapeutic effects. From this point of view, steroids and immunomodulatory drugs appear to be among the most useful drugs.

Topical steroids are the most effective drugs for achieving a quick remission of inflammation, and have been used for decades. How-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 45–49).

ever, the number of AD patients with local adverse reactions due to long-term use of topical steroids, with intractable AD lesions resistant to topical steroids, and with AD eruptions on the face and neck, where long-term use of topical steroids is difficult, is increasing. As a result, there has been an increasing demand for the development of drugs that exert their anti-inflammatory and anti-allergic actions through different mechanisms from those of steroids.

Under such circumstances, immunomodulatory drugs have been developed to provide a new approach to the treatment of AD. In this article, discussion will be focused on topical FK 506 (tacrolimus), which is an immunomodulatory drug introduced recently for the treatment of AD, and the expected roles of this drug on the treatment of AD in the future.

Role of Steroids and the Problems Associated with These Drugs in the Treatment of AD

The Japanese guidelines for the treatment of AD by pharmacotherapy basically recommend the use of topical steroids for the treatment of eczematous lesions. This is based on the observation of the excellent efficacy of topical steroids in effecting a quick cure in eczema. However, the following precautions are listed for the use of topical steroids: 1) Selection of the type, strength, and amounts of the topical steroids should be based on the severity, location and characteristics of the eczematous lesions, and the patients' age. 2) As a general rule, the use of topical steroids on the face should be avoided. If it is inevitable, weak preparations should be used for the shortest duration possible. 3) The severity of the lesions should be evaluated every week, and switching of the drug should be considered. As a general rule, only physicians with a good understanding of the characteristics and effects of these drugs should be allowed to prescribe topical steroids.

The problems associated with the use of topical steroids include the occurrence of local adverse reactions, such as skin atrophy, telangiectasia, and hypertrichosis. These may result from long-term use, or use in areas susceptible to local adverse reactions, such as the face and neck.

Therefore, topical drugs that exert similar anti-inflammatory and anti-allergic actions via different mechanisms from those of topical steroids, and that do not elicit the local adverse reactions observed with topical steroids, are urgently needed. It is in this background that topical tacrolimus came to be developed.

Actions of Tacrolimus

In 1984, tacrolimus was discovered as a compound with a macrolide skeleton produced by *Streptomyces tsukubaensis*. With a molecular weight of 822.05, it is a much smaller molecule than cyclosporin, which exerts similar actions and has a molecular weight of 1202.63. It acts mainly during the early stage of T-cell activation. It accomplishes efficient immunosuppression by inhibiting the expression of cytokine genes, which play important roles in immune responses.

The drug binds to calcineurin, a dephosphorylation enzyme activated in the presence of Ca^{+} and calmodulin, and inhibits its actions, thereby inhibiting the translocation of a T-cell-specific transcription factor (NF-AT) subunit (NF-ATc) from the cyto-plasma to the nucleus. In this way, the drug is believed to inhibit the expression of such cytokine genes as that of IL-2.[1] Therefore, unlike steroids, it does not induce skin atrophy.

The mechanisms underlying the therapeutic actions of tacrolimus on AD are as follows: 1) inhibition of cytokine production and release from Th1 cells and Th2 cells[2]; 2) disruption of the antigen-presenting ability of Langerhans cells; 3) inhibition of IgE-dependent histamine release from mast cells and basophils; 4) inhibition of degranulation of eosinophils; and 5) inhibition of cytokine-induced chemokine production from epidermal cells and fibro-

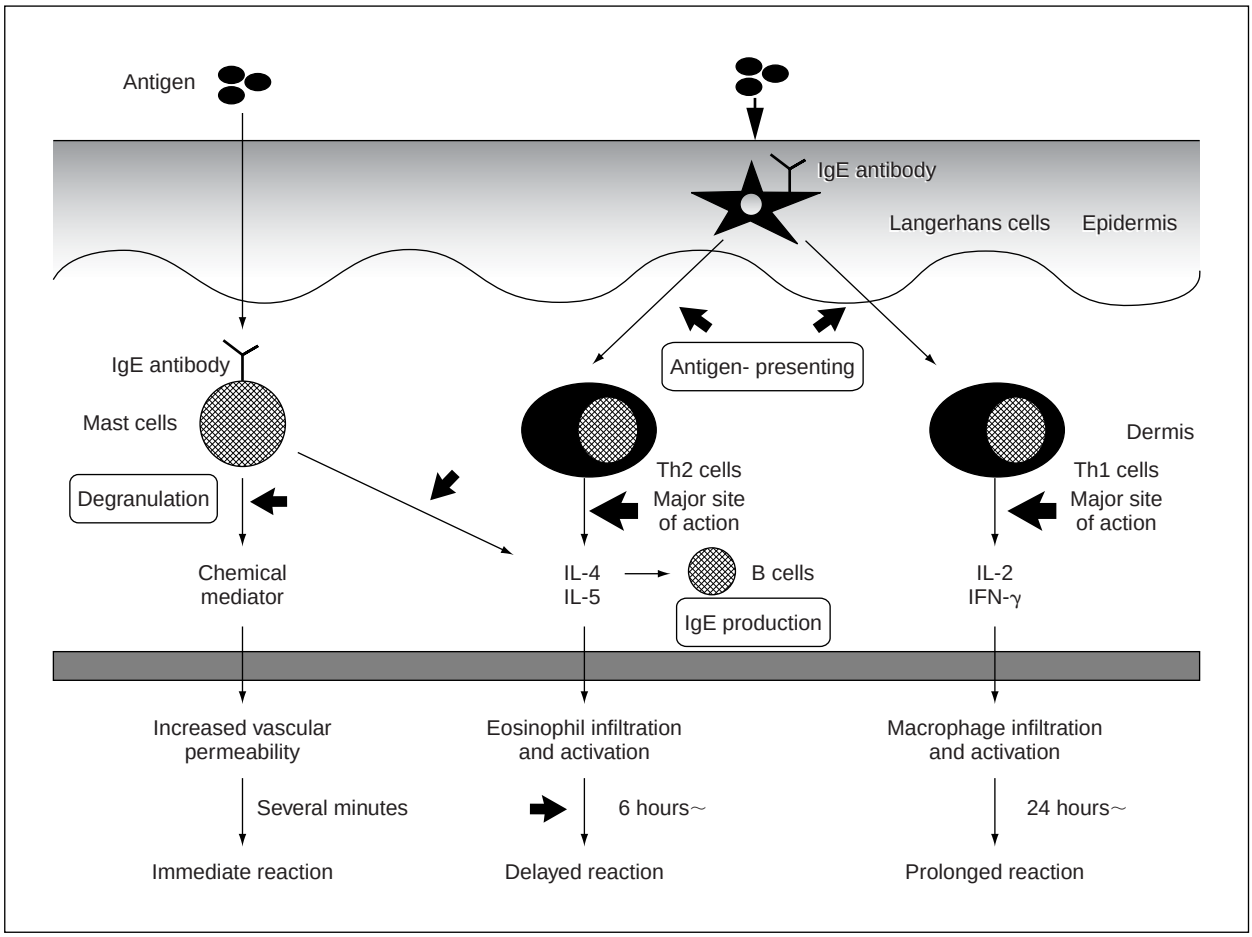


Fig. 1 Mechanism of development of atopic dermatitis and sites of action of tacrolimus
- Site of action is indicated by an arrow.
- The main mechanism of action is inhibition of the expression of cytokine genes by inhibition of the intranuclear translocation of a T-cell specific transcription factor, and the resultant suppression of T-cell activation.

blasts (Fig. 1).

Results of Treatment of AD with Topical Tacrolimus

At present, the use of 0.1% tacrolimus ointment for the treatment of AD in adult patients is covered by insurance in Japan. Its clinical efficacy has been demonstrated to be significantly superior to that of 0.1% alclometasone dipropionate ointment against eruptions on the face and neck,[3] and to be almost equivalent to that of 0.12% betamethasone valerate ointment against eruptions on the trunk and extremities.[4] It is noteworthy that skin atrophy and telangiectasia, local adverse reactions with topical steroids, gradually resolved with the long-term use of tacrolimus ointment.

A problem associated with this ointment, however, is the high incidence of transient skin irritation symptoms after its application, associated with erythema and a burning sensation, pain, and itching. These symptoms occur at a particularly high incidence when the ointment is used for eruptions on the face and neck.[5] Most of these symptoms are transient (about 3 or 4 days) and mild or moderate, and disappear immediately upon remission of the eruptions.

However, it is important to explain to the patient in advance about the possibility of appearance of these symptoms of skin irritation with the ointment application.

Another problem associated with this ointment is that topical application of the ointment over an extensive area may lead to elevated blood concentrations of the drug and the risk of occurrence of systemic adverse reactions. In a study in which a total of 20 g/day of 0.1% ointment was used (10 g at a time, an amount sufficient for application over the whole body), a blood concentration of 20 ng/m*l* was detected in one of 3 AD patients.[6] However, the percutaneous absorption of the drug in this patient decreased as the eruptions remitted, associated with an immediate decrease in its blood concentration. A week later, the blood concentration was found to have decreased to below 4 ng/m*l*. Thus, the elevated blood concentration associated with the ointment application over an extensive area of the body is transient and believed to be not problematic. However, some precautions must be addressed in patients in whom remission of the eruptions is not achieved even after prolonged high-amount topical use. Precautions must also be addressed when the barrier functions of the skin are markedly impaired, because in such a situation, the systemic absorption of the drug may be markedly accelerated.

In another study in which tacrolimus ointment was applied over the whole body for a prolonged period (observation for more than 12 months), a low concentration of the drug was detected in the blood, although not very frequently, when about 10 g/day was applied topically in patients with severe eruptions. In this study, however, no problematic systemic adverse reactions were reported in any of the 568 subjects examined.[7] Thus, the use of the drug over a limited area or for prolonged periods of time, especially when the eruptions remit within a short period of time, does not appear to be associated with any clinical problems. However, in consideration of safety, the maximal dose of tacrolimus ointment should be limited to no more than 10 g/day.

Another problem is complicating infection. According to clinical studies conducted to date, folliculitis is noted at the highest incidence (about 10%), but the condition remits rapidly with oral and topical administration of antibacterial drugs. The incidence of the infection did not exceed this percentage when the drug was used for prolonged periods.

As to other types of infection, Kaposi's varicelliform eruptions (KVE) induced by widespread percutaneous inoculation of herpes simplex virus (HSV) was reported at an incidence of 4% in the 568 subjects followed for a prolonged period.[7] The incidence of KVE is believed to have increased in recent years with the increase in number of AD patients, and the condition has become more severe. In a narrow sense, KVE is defined as a condition that is associated with systemic symptoms, including fever, general fatigue and multiple, relatively large blisters. However, conditions with relatively mild symptoms induced by re-infection are also regarded as KVE in Japan (broad definition). The annual incidence of KVE among AD patients in Japan is estimated to be about 7%.

The association between the use of immunomodulatory drugs in AD and the occurrence of KVE is unknown. However, one study suggested an estimated annual incidence of 5.6% in 568 subjects receiving tacrolimus ointment application (incidence of KVE by the narrow definition was about 4%). Therefore, at present, the use of topical tacrolimus does not appear to be associated with an increased incidence of KVE. However, it goes without saying that precautions must be addressed to ensure early detection and early treatment of this condition.

Based on the results of studies on the use of tacrolimus ointment to treat pediatric AD patients, a 0.03% ointment was developed and is now commercially available in the United States. In Japan, clinical studies have been conducted on the use of this ointment for AD in

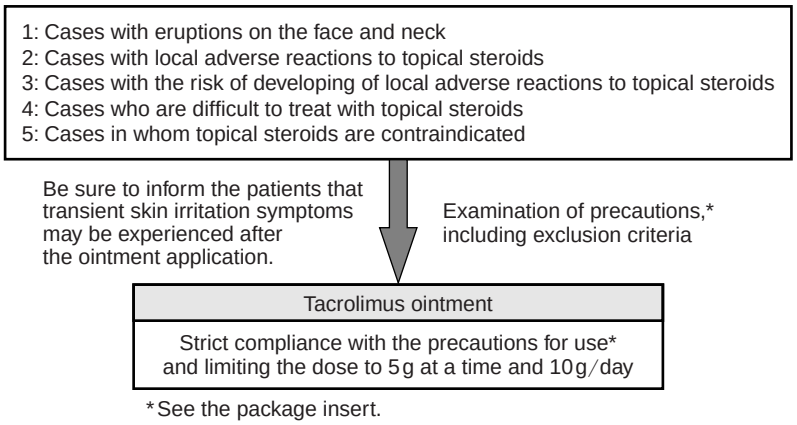


Fig. 2 Flow chart of the use of tacrolimus ointment in patients with atopic dermatitis aged over 16 years

children (ranging in age from 2 to 15 years). Thus, the use of the drug in children may also be covered by insurance in the near future. Moreover, the development of another macrolide immunomodulatory drug, topical ascomycin, is under way, although its efficacy may be inferior to that of tacrolimus.

Figure 2 shows the flow chart for the use of tacrolimus ointment in the treatment of AD.

Combined Use of Topical Steroids and Tacrolimus Ointment

Topical steroids, especially those with high potency, are known to be useful for achieving prompt remission of the inflammation in AD; however, prolonged use may be associated with local adverse drug reactions, including skin atrophy. Tacrolimus ointment has a relatively limited efficacy, however, it is more suitable for prolonged use. In the clinical setting, it is recommended that these characteristics of the two drugs be used to advantage, and that the drugs be combined to obtain good efficacy.[8] Specifically, it is possible to reduce the skin irritation symptoms induced by tacrolimus ointment by first using relatively high-potency topical steroids for a short period to sufficiently reduce the inflammation, and then switching to tacrolimus ointment to avoid local adverse reactions.

Treatment of AD by Oral Cyclosporin

Treatment with oral cyclosporin (maximum dose: 5 mg/kg/day) is covered by insurance in Europe and Canada only in cases with severe intractable adult patients with AD, resistant to conventional treatments, and in whom the condition markedly impairs the patients' QOL.[9,10] Its excellent efficacy has been demonstrated, and clinical studies of the drug have been started in this group of patients in Japan. However, considering the potential risk of occurrence of renal dysfunction, increased blood pressure and various diseases associated with persistent immunosuppression with prolonged use of oral cyclosporin, it is recommended that the drug be administered for as short a period as possible, only until treatment by a more conventional approach becomes feasible.

Conclusion

When used appropriately, topical steroids are the most effective drugs for the treatment of AD. However, in the case of patients with intractable AD resistant to topical steroids, patients with eruptions on the face and neck, where prolonged application of topical steroids

is difficult, and patients vulnerable to the local adverse reactions to topical steroids, the combined use of topical steroids and tacrolimus ointments is believed to be useful for improvement of the QOL in AD patients.

REFERENCES

1) Tamura, J., Kawada, E. and Matsumoto, M.: Molecular mechanism of immunosuppression by cyclosporin A and FK 506 — With emphasis on the target enzyme, calcineurin. *Jikkeni* 1993; 11(7): 41. (in Japanese)
2) Mori, A. *et al.*: Regulation of interleukin-5 production by peripheral blood mononuclear cells from atopic patients with FK 506, cyclosporin A and Glucocorticoid. *Int Arch Allergy Immunol* 1994; 104(suppl): 32–35.
3) FK506 Ointment Study Group: Phase III comparative study of FK506 ointment — Randomized double-blind comparison study with alclometasone dipropionate ointment against atopic dermatitis (face and neck) —. *Hifuka Kiyo* 1997; 92: 277. (in Japanese)
4) FK506 Ointment Study Group: Phase III comparative study of FK506 ointment — Randomized double-blind comparison study with betamethasone valerate ointment against atopic dermatitis (trunk and extremities) —. *Nishinihon Hifuka* 1997; 59: 870. (in Japanese)
5) Nakagawa, H. *et al.*: Tacrolimus ointment for atopic dermatitis. *Lancet* 1994; 344: 883.
6) Kawashima, M. *et al.*: Tacrolimus concentrations in blood during topical treatment of atopic dermatitis. *Lancet* 1996; 348: 1240–1241.
7) FK506 Ointment Study Group: Long-term observation study of FK506 (tacrolimus) against atopic dermatitis — One-year results —. *Rinsho Iyaku* 1998; 14: 2405. (in Japanese)
8) Ruzicka, T., Assmann, T. and Homey, B.: Tacrolimus: The drug for the turn of the millennium? *Arch Dermatol* 1999; 135: 574–580.
9) Camp, R.D., Reitamo, S., Friedmann, P.S. *et al.*: Cyclosporin A in severe, therapy-resistant atopic dermatitis: Report of an international workshop, April 1993. *Br J Dermatol* 1993; 129: 217–220.
10) Salek, M.S., Finlay, A.Y., Luscombe, D.K. *et al.*: Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 1993; 129: 422–430.

Problems Associated with Inadequate Treatment for Atopic Dermatitis

JMAJ 45(11): 483–489, 2002

Kazuhiko TAKEHARA

Professor, Department of Dermatology, Kanazawa University School of Medicine

Abstract: Widespread confusion currently exits in Japan with regard to the treatment of atopic dermatitis, creating a difficult social problem. As a background to this confusion, the mass media have been highly critical of topical steroids and have given the general public the idea that steroid ointments are dangerous, although proper use of these ointments is essential for the treatment of atopic dermatitis, as is commonly recognized throughout the world. A so-called "atopy industry" has sprung up in which alternative remedies are used to treat atopic dermatitis, creating large numbers of patients with severe problems resulting from inadequate methods of treatment. In 1998, the Japanese Dermatological Association (JDA) organized a committee to survey the health damage caused by inadequate treatment of atopic dermatitis, and the committee published its final results in 2000. Among 310 severe cases, a surprisingly high 140 cases (44%) were worsened by inadequate treatment, whereas only 3 patients suffered from side effects of steroid ointment treatment. The JDA organized a new committee in June 2000, to examine the problems of treatment in atopic dermatitis. One of the major activities of this committee is direct consultation with patients via e-mail and facsimile. After the initiation of this system, the committee has received 1,504 requests for consultation within 9 months. Dermatologists need to exert much greater effort to solve this social problem.

Key words: Atopic dermatitis; Atopy industry; Topical steroids; Inadequate treatment

Introduction

The phrase "atopy industry" (lit. "atopy business") is well recognized in Japan, where widespread inadequate treatment of atopic dermatitis in this country has been widely reported by the mass media. It is astonishing that inadequate treatment of atopic dermatitis is so widespread in Japan, despite the fact that atopic dermatitis is a common disease for

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 53–57).

which a global standard of treatment has been established.

Why are such large numbers of patients suffering from severe health problems induced by inadequate treatment, to the extent that normal social life is sometimes interrupted? Why do patients still blindly believe that their problems are part of the natural process of healing or are created by the use of topical steroids, instead of recognizing them to be the result of inadequate treatment?

It is the task of dermatologists in clinical practice to clearly educate patients who are suffering the health hazards of inadequate treatment. This is also a problem to be addressed by the Japanese Dermatological Association (JDA), to reach the increasing numbers of patients who refuse to visit a medical facility and instead withdraw from society.

Inadequate Treatment of Atopic Dermatitis

A variety of information and misinformation about the medical treatment of atopic dermatitis is currently flooding Japan, creating a great deal of confusion throughout the society. During the past decade, the adverse effects of topical steroids, essential medicaments in the treatment of atopic dermatitis, were repeatedly exaggerated by the mass media, including the press, TV, and periodicals, creating confusion and anxiety among patients with atopic dermatitis who were receiving orthodox treatment in a medical facility or who were about to receive such treatment. In parallel with this phenomenon, a booming industry that advocates folk remedies and special alternative therapies has developed. This industry is referred to by many as the "atopy industry". Consequently, increasing numbers of patients have developed an irrational fear of topical steroids, while choosing to depend solely on folk remedies or alternative methods of healing, thereby markedly worsening their symptoms and creating difficulties in leading a normal social life.[1–4)]

Although folk remedies and alternative therapies cannot necessarily be equated with inadequate treatment, the numbers of patients who have markedly worsened symptoms or who have complications after treatment by a nonspecialist or unqualified care provider are continuing to increase. "Inadequate treatment" used here refers to treatment such that its aggressive implementation results in a worsened clinical picture for the patient.

This situation in which patients request folk remedies and alternative therapies at the expense of topical steroids is unique to this country. In other developed countries, medical care by specialists who prescribe topical steroids is well accepted by the general population. For the treatment of bronchial asthma, which is categorized as an atopic disease like atopic dermatitis, a worldwide consensus has been reached as to the usefulness of inhaled steroid therapy, i.e., local administration of a steroid aimed at early relief of airway inflammation. In contrast, it is highly unusual that the similar use of topical steroids aimed at the early relief of skin inflammation has been the focus of a number of criticisms in Japanese society.

Behind this social confusion, lies a prosperous "atopy industry" that targets patients with atopic dermatitis. The actual situation of this industry is also discussed in this paper.

Reasons for the Spread of Inadequate Treatment

Why has the inadequate treatment of atopic dermatitis spread to this extent? The following factors were noted in an analysis of the background of the situation.

(1) Medical firms that were targeting various chronic diseases entered the area of atopic dermatitis in large numbers, deeming it a good market because information was confusing.

(2) Patients and the mass media, believing atopic dermatitis to be an intractable disease, sought alternative remedies and eschewed the standard treatment.

(3) The adverse effects of topical steroids were exaggerated, and symptom aggravation caused by inadequate treatment was taken to be an adverse effect of topical steroid therapy.

(4) Medical facilities touting nonsteroidal treatments increased as a result of mass media portrayal as "patient-oriented medical providers".

(5) In some cases, the combined use of topical steroids was covered up when the therapy was publicized by the mass media, even though steroids were actually part of combined treatment (e.g., Isodine therapy, *Bihadasui* therapy).

(6) Disagreement between dermatologists and pediatricians in regard to their views on the pathogenesis and treatment caused anxiety among patients, leading them to seek inadequate, alternative treatment, even those that deviated from the recommended treatments of both disciplines.

Survey of Health Damage from Inadequate Treatment

To prevent the increase of adverse health consequences owing to the use of folk remedies and alternative therapies in the treatment of atopic dermatitis, JDA in October 1998 organized a committee, headed by the author, to survey the actual situation resulting from inadequate treatment of atopic dermatitis. The nationwide survey was carried out over one year in 11 university hospitals. Inadequate treatment was defined as treatment that caused worsening of the clinical picture of the patient after its active use. The survey was not intended to evaluate the usefulness of individual treatments. Details of the final results of the survey were published in the June 2000 issue of "*Nippon Hifuka Gakkai Zasshi (Journal of the Japanese Dermatological Association)*".[4)]

The one-year survey revealed 349 severe cases that necessitated hospitalization at the 11 facilities. Excluding 30 patients who were admitted for educational purposes, the remaining 319 patients included 140 (44%) patients in whom the condition was aggravated because of inadequate treatment. In addition, 127 (40%) patients had spontaneous aggravation, 32 (10%) patients were reluctant to receive treatment, and only 3 (1%) patients suffered adverse effects of topical steroids.

Inadequate treatment was given to 52 (37%) patients by physicians other than dermatologists, and to 37 (26%) patients by dermatologists, accounting for 63% altogether.

Issues involved in inadequate treatment included:

- Prevalence of alternative therapies administered by non-specialists
- Mass media reporting of prescriptions being given by physicians in the absence of any medical examination
- A tendency toward excessive dependence on Chinese medicine
- Persistence of highly restricted diet therapy
- Increased use of nonsteroidal therapy by non-dermatologists.

The consequences of inadequate treatment were found to include a number of cases of withdrawal from society, reflected in 40 (29%) cases in which a leave of absence was taken from school or work or in which the individual quit school or a job, and 21 (15%) cases of withdrawal by staying at home.

Survey of Alternative Therapies by the Department of Dermatology, Kanazawa University School of Medicine

A survey was carried out in 191 patients with atopic dermatitis who were being treated at our atopic outpatient clinic, to examine their experience with alternative therapies. An outline of the survey is given below.

(1) Patients who had used an alternative therapy accounted for 84% of all subjects.

(2) The average number of sessions of alternative therapy experienced per patient was 5.1.

(3) Table 1 summarizes the patients' impressions of such therapies. The majority of patients

Table 1 Patients' Experiences in the Atopy Industry by Category and Impressions of Efficacy

Therapy	Number of patients who experienced (total 191)		Total number of cases	Effective	No change	Aggravated
Health food and related remedies	100	52.4%	228	8.8%	84.2%	7.0%
Spa and bathing treatments	92	48.2%	151	15.9%	65.6%	18.5%
Cosmetics and related remedies	83	43.5%	144	4.9%	64.6%	30.6%
Anti-mite and related remedies	73	38.2%	109	24.8%	74.3%	0.9%
Water therapy and related remedies	47	24.6%	57	1.8%	75.4%	22.8%
Medical institution-related alternative therapies	34	17.8%	35	8.6%	20.0%	71.4%
Other alternative therapies	67	35.1%	101	8.9%	63.4%	27.7%

Patients who experienced more than one type or session of treatment provided their impressions of efficacy of each type or session, and the percentages were calculated over the total number of cases in the population.

reported that their condition was "unchanged" or "aggravated". In particular, aggravation was conspicuous for the use of cosmetics, water therapy, and alternative therapy by a medical institution. Only anti-mite therapy held potential benefit.

(4) About half of the patients replied that they were victims, in one way or other, of the alternative health care industry.

(5) To the question of whom should be blamed for the current prevalence of ineffective alternative therapies, the mass media was most often mentioned (31%), followed by dermatologists who did not provide sufficient information (19%).

What is the "Atopy Industry"?

It is apparent that alternative treatments for atopic dermatitis can cause serious harm to patients. It is therefore worth exploring this industry in detail.

The "atopy industry" is defined as "economic activities that are involved in the treatment of atopic dermatitis by means of actions not covered under health insurance, targeting patients with atopic dermatitis".

Use of the term "atopy industry" rather than "folk remedies" provides a better understanding of the current situation of treatment for atopic dermatitis. Folk remedies originally are extensions of people's personal experience and the wisdom of ancestors and the elderly. They imply tradition and goodwill. However, most current "folk remedies" are purveyed by commercial enterprises aimed at making profit in a capitalist economy. In addition, in some cases, certain expensive products are sold via medical practices in hospitals managed by a related company, or by doctors who recommend a certain folk remedy that they are advocating. Therefore, the boundaries between folk remedies and medical practice are nebulous.

The aforementioned definition of the "atopy industry" is intended to include such activities practiced or supported by medical facilities and doctors.

Are Alternative Therapies Effective?

Alternative therapies that are unlikely to be effective are nevertheless described as "dramatically effective". The following points indicate how ineffective therapies can be seen in consumers' minds as effective.

(1) Extravagant advertising: Exaggerations

Table 2 Consultation System for Atopic Dermatitis Patients

Patient consultation system provided by the Japanese Dermatological Association
FAX (dial-in): +81-(0)76-234-4274
e-mail: atopic@med.kanazawa-u.ac.jp
URL of the Committee for Treatment Problems in Atopic Dermatitis of the Japanese Dermatological Association: http://web.kanazawa-u.ac.jp/~med24/atopy/therapy.html
Defense Counsel for Atopy Industry Victims
URL: http://homepage2.nifty.com/atopy/
e-mail: atopiclaw@livedoor.com

and overstatements are the nature of commercial advertising.

(2) Spontaneous remission: Patients may believe that there is no spontaneous remission of atopic dermatitis and therefore view such remission as treatment-related.

(3) Effect of suggestion: The more expensive the therapy, the greater the belief in its efficacy.

(4) Elimination of aggravating factors: When treatment involves aggravating factors, its discontinuation inevitably improves the patient's condition.

(5) Incomplete data: The efficacy of folk remedies is usually backed by testimonials or personal experience rather than scientific evidence.

(6) Exclusion of aggravated cases: All aggravations tend to be attributed to the adverse effects of previously used topical steroids.

(7) Combined use of steroids: In alternative therapies implemented through medical facilities, steroids tend to be combined with the alternative treatment, and this may not be recognized by the patient.

Problems Inherent in the "Atopy Industry"

The reader may be unaware that a death resulting from alternative therapy for atopic dermatitis has already occurred in this country. An "atopy detergent" developed by a certain metal finishing company was publicized in a community bulletin as a remedy for atopic dermatitis. A 4-year-old boy who used this agent eventually died of methemoglobinemia.

The following is a summary of problems involved in the alternative treatment of atopic dermatitis.

(1) Patients are not given correct information about the disease and its treatment.

(2) Alternative remedies may themselves serve as aggravating factors.

(3) Medical care may be given by unlicensed practitioners.

(4) Unreasonably high prices may be charged.

(5) Liability is unclear in comparison with that for treatment obtained through proper medical channels.

Committee for Treatment Problems in Atopic Dermatitis

To counter the confusion surrounding medical care for atopic dermatitis, JDA, acting on behalf of Japanese society, in June 2000 set up a committee to examine problems associated with the alternative treatment of atopic dermatitis. This expanded committee unified two committees previously established in 1998 (committee on the development of treatment guidelines for atopic dermatitis, committee for the

survey of health damage caused by inadequate treatment of atopic dermatitis), for the purpose of addressing a wider range of issues in the treatment of atopic dermatitis.

The chief activities of the committee are as follows.

- Patient consultation via dial-in facsimile and e-mail (Table 2).
- Extensive survey of health damage resulting from inadequate treatment.
- Review and promotion of treatment guidelines.
- Examination of issues surrounding new therapeutic drugs (e.g., tacrolimus ointment).
- Survey of the current situation of damage through consumer centers.
- Survey of information about atopy on the Internet.
- Publicity activities directed to the general public.

The above activities of the committee are intended to continue until April 2002.

Consultation System for Atopic Dermatitis Patients

In July 2000, JDA began a consultation system for patients suffering from atopic dermatitis. This system was introduced in the July 7, 2000, issues of the Asahi and Yomiuri newspapers. About 200 applications for counseling were received in the following two days, with the number reaching 616 by the end of the month (425 cases by e-mail, 189 by facsimile, and 2 by letter) and 1,504 by March 2001. Problems related to inadequate treatment accounted for about 20% of all requests for consultation.

Emergency Call for Atopy Industry Victims

In response to the increasing number of victims of the atopy industry and occasional lawsuits, a defense counsel for atopy industry victims was organized by a group of concerned young lawyers, and an emergency call system for victims of the atopy industry was implemented by the counsel on August 5, 2000, in a law office in Tokyo, with medical advice provided by dermatologists. Following that, a consultation service was set up via the Internet. In addition, in May 2001, a plaintiff represented by the lawyer Shinnosuke Fukushima, the leader of the above-mentioned defense counsel, won the first lawsuit against the atopy industry by defeating an esthetic service provider. The verdict was widely reported in the mass media.

The Fight Against the Atopy Industry

The greatest responsibility for the spread of the atopy industry rests not with the mass media or patients themselves, but with doctors who deal with the treatment of atopic dermatitis. Medical care providers have been slow to take action against the industry, and more than a few have actually joined forces with it.

What should be done to win the fight against this unscrupulous industry? This is a question that needs to be addressed.

The most important elements are that better, more informative explanations be given to patients and that treatment be carried out with perseverance in daily medical practice. While patients naturally want rapid relief, they need to be told clearly and understandably that atopic dermatitis is a chronic disease characterized by the cardinal symptom of skin inflammation. They need to understand that long-term control of the inflammation is necessary, mainly through the use of topical steroids. This principle should be emphasized, and should be clearly understood by the patient. Doctors who treat patients with atopic dermatitis should not disregard the basics of treatment for skin disease, i.e., to choose topical drugs that suit the pathological condition. If they fear the adverse effects of topical steroids and perform nonsteroidal therapy in a careless way, with the excuse that the patient her- or himself has requested it, ultimately they may suffer loss of

the patient's trust.

It is also necessary for medical care providers to have a thorough understanding of the actual situation and tactics of the atopy industry and to take measures to deal with these tactics. As mentioned previously, the JDA widely publicized through the mass media the results of a survey on the actual damage caused by the atopy industry, and have attempted to correct the public's rigid and biased attitude that steroids used for the treatment of atopic dermatitis are "evil drugs". The efforts of JDA are now producing successful results, although more remains to be done.

REFERENCES

1. Takehara, K.: A private view of the atopy industry: Investigation by a dermatologist. Sentanigakusha, 1998. (in Japanese)
2. Takehara, K.: A private view of the atopy industry, 2: Subsequent investigation. Sentanigakusha, 2000. (in Japanese)
3. Takehara, K.: Atopy industry. Bungeishunjusha, 2000. (in Japanese)
4. Takehara, K. *et al.*: Survey of the health damage caused by inadequate treatment of atopic dermatitis (final report). *Nippon Hifuka Gakkai Zasshi* 2000; 110: 1095–1098. (in Japanese)

Atopic Dermatitis: Psychological Care

JMAJ 45(11): 490–495, 2002

Ryoichi KAMIDE

Assistant Professor, Department of Dermatology, Jikei University School of Medicine

Abstract: The number of adult atopic dermatitis patients have increased in recent years. Distrust of medical care arising from the abuse of topical steroids has given rise to a flourishing so-called "atopy business", and this has imposed physical, mental, and financial burdens on the patients. The Japanese Dermatological Association has prepared diagnostic criteria and treatment guidelines to eliminate this situation, and in the process the psychosocial aspects of atopic dermatitis have been taken up as exacerbating factors. Scratching associated with emotions starts when the anger, anxiety, impatience, and tension that arises from the stress in daily life is released, and scratching behavior is established. This is characterized by the appearance of bilaterally symmetrical eczematous rash lesions over the areas of the body that the hands can reach. The first step in the clinical care of atopic dermatitis patients is making them aware of the fact that their idiosyncratic scratching is the greatest factor in prolonging the symptoms. Accordingly, it is important to listen attentively with a receptive and empathetic attitude to the stress the patient is experiencing. An integrated clinical strategy that combines "proper drug therapy" with "psychological care" is needed.

Key words: Atopic dermatitis; Psychological care; Psychosomatic medicine; Scratching behavior

Introduction

The atopic dermatitis that we have been encountering recently is highly intractable, and the number of patients in whom it persists into adulthood has been increasing. In addition to the problem of patients' appearance, it is associated with lack of sleep because of intense itching, and there is also considerable loss of QOL in terms of patients' going about their lives in society. For these reasons, atopic dermatitis is one of the skin diseases for which the establishment of an appropriate method of treatment is strongly desired.

Before the name "atopic dermatitis" was advocated by Sulzberger *et al.* in 1933, in Europe the disease was called constitutional eczema, neurodermatitis, and Besnier's prurigo. The pathological elucidation of atopic dermatitis subsequently progressed in tandem with the

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 1, 2001, pages 59–62).

evolution of immunology and allergology. By contrast, although there was considerable debate concerning the psychological aspects of atopic dermatitis and psychosomatic approaches in the 1940s, it was later overshadowed by allergy research, and for all practical purposes hardly anything was ever done about it. Lately, however, the psychosomatic approach to atopic dermatitis has been taken up in large measure, and this trend has placed more weight on curing patients who have the disease than on elucidating its pathology.

Circumstances Surrounding Atopic Dermatitis

One of the reasons why the psychosomatic approach to atopic dermatitis has come to attract so much attention has been the public's criticism of the abuse of topical steroids, which ironically have been the main pillar of the treatment of atopic dermatitis. Adverse reactions have been revealed as a result of long-term use of topical steroids, and this coupled with excessive reporting in the mass media, has led to the steroidphobia and intense distrust of medicine. This gap has been associated with the rampant growth of the so-called "atopy business",[1] and not knowing what to believe, the patients and their families have been at the mercy of dubious information and have been subjected to physical, psychological, and financial burdens.

To overcome this situation, the Japanese Dermatological Association has published the "Diagnostic Criteria for Atopic Dermatitis" and "Treatment Guidelines for Atopic Dermatitis".[2] The latter is published for specialists in dermatology, and one of the noteworthy features is that it takes up the psychological aspects of the disease. More specifically, numerous exacerbating factors are involved in prolonging atopic dermatitis. Despite avoiding allergens, such as certain foods and mites, and performing skin care that corrects abnormal barrier function, atopic dermatitis usually fails to respond to routine clinical care. This signifies that some other factor has been overlooked in the present clinical practice for atopic dermatitis.

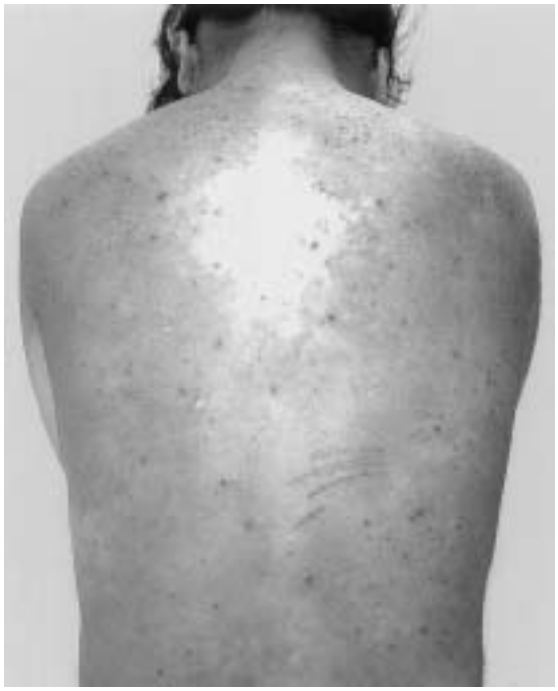


Fig. 1 Butterfly sign
The skin rash produced by scratching is visible only in the areas where the patient's hands can reach.

Habitual Scratching

A psychosocial factor, idiosyncratic scratching behavior caused by the stress of everyday life, has been recognized as one of the answers. Kobayashi[3] used diaries to analyze the scratching behavior of a large number of atopic dermatitis patients, and was the first to point to the contribution of habitual scratching in formation of the lesions of atopic dermatitis. The scratching is patterned, with the rash exhibiting a bilaterally symmetrical distribution over the back and normal skin remaining in the middle where the hands cannot reach, producing a "butterfly" sign (Fig. 1).

The scratching often begins automatically in association with emotions, and it is performed habitually every day. In addition to the psycho-

logical factors, such as anger, irritation, impatience, relief, anxiety, etc., many patients say that they somehow find themselves scratching even when they do not itch. The prominent red face in adult-type atopic dermatitis can also be explained by this scratching behavior.

Higaki *et al.*[4] conducted a questionnaire survey and found that psychosocial factors contributed to exacerbating atopic dermatitis in 83% of patients 16 years of age and older. In our study as well[5] psychosocial factors contributed in the form of exacerbating factors in 29 (93.5%) of the 31 adult atopic dermatitis patients who required hospitalization.

The most common psychosocial factors identified were attributable to excessive demands on the patient's time at work, at school, at home, etc., taking examinations, and mother-child relations. However, no contribution by psychosocial factors was identified in about 10% of the patients, and another approximately 10% had obvious mental disorders, such as panic disorder or depression. We therefore concluded that approximately 80% of atopic dermatitis patients form a group that is capable of responding to psychosomatic care, more specifically, to attentive listening. It appears that these psychosocial factors may prolong atopic dermatitis through habitual or idiosyncratic scratching.

Psychological Characteristics of Atopic Dermatitis Patients

In this way psychosocial factors have been found to have a major influence in inducing and prolonging scratching, but do atopic dermatitis patients display any special psychological characteristics? Several studies have assessed this question, and the results are summarized that the patients display severe anxiety and depression, and they tend to have a high level of anger.[6] It remains unresolved whether these psychological characteristics are truly specific to atopic dermatitis, or whether the presence of atopic dermatitis itself produces this sort of psychological state. In any event, telling patients, "You have these psychological tendencies", probably does not help. Of course, psychotherapy or psychiatric treatment does not need to be considered at the very beginning. What is most important is to make the patient aware that the habitual scratching is the greatest causative factor in prolonging the symptoms. The first thing required to be able to achieve this is attentive listening.

Holistic Understanding of the Patient Centered on Attentive Listening

While attentive listening is important, examinations start with careful identification of the physical manifestations. If possible, with curtain drawn, etc., inspect the patient's entire body, check the distribution and severity of the skin rashes, and even in areas where there are no obvious skin lesions actually touch the skin to determine whether it tends to be even slightly dry, or whether any moist normal skin remains at all. Conversations that encourage the patient to a complete cure, for example by saying something like, "Since you still have this really clear skin, if we treat it properly, all of your skin should clear up", are useful especially during palpation of the normal skin. Palpation allows the physician to determine the state of the patient's skin and at the same time send a message to the patient through the physician's touch.

Checking for rashes caused by scratching, which are considered characteristics of atopic dermatitis, such as the "butterfly sign" described above, glossy nails, referred to as "pearly nails" (fingernails made shiny by scratching), pigmentation and thickening of the dorsal aspects of the finger joints (evidence of using those areas to scratch other sites), bilateral pityriatic erythema of the neck (having simultaneously rubbed it with the thumb and middle finger), pityriatic erythema in the midline of the neck (pinching with the thumb and the index finger), Hertoghe's sign (thinning of approximately the

lateral 1/3 of the eyebrows) provides objective evidence when attempting to convince the patient of habitual scratching later.

Sitting at a 90 degree angle from the patient creates better conditions for talking during the medical interview than sitting directly opposite the patient. Have the patient talk about the course of the atopic dermatitis thus far, if possible, describing it in chronological order, asking when it began, and when it grew worse. Ask about treatment during that period and whether anything seemed to aggravate it, however, it is essential to express an empathetic attitude, by saying something like, "That must have been terrible".

Inquire about psychological conditions at home (husband-wife, parent-child, wife-mother in law relations), schoolwork (friends, examinations, cram school, clubs), work-related stress (job-hunting, overtime, sleeplessness, qualitatively difficult work) as psychosocial factors that are often involved in exacerbations. While touch on a variety of matters during the conversation, find out whether the patients have had a so-to-speak "exhausting" time of it, and whether the patient has been put in a position of "being unable to be convinced". Check on family composition and others living in the home by starting out by asking whether anyone has had any eczematous rashes, and then casually broadening the conversation. Since it is sometimes difficult for the patients themselves to mention, for example, that they are divorced, or that their parents are living separately, it is better to ask about the family situation after the conversation has progressed somewhat. If the patient is employed, it is easier for the patient to accept when the conversation starts with work.

As the topic of conversation gets closer to the core, the patients' hands automatically begin to touch their arms and neck. If you restrain their hand and say "This is the problem", most patients look surprised and suddenly become aware of their unconscious scratching. At the first meeting, it takes the patients about 20 minutes before they begin to talk about what is troubling them most, yet that is the most important part in terms of obtaining their "awareness", and it forms the foundation for physician-patient relations and a trusting relationship.

This attentive listening is also meaningful as a form of counseling. Its most important aspect is the caregivers' attitude being receptive and empathetic, and striving not to judge the patients according to their own personal values. Physicians usually occupy a high position in society and have a tendency to brand patients as psychologically weak from their superior position, as though they were judges, however, they must be strictly admonished against speech that might invite the patients to react in that manner.

Mothers of children with atopic dermatitis often lose confidence in their childrearing ability and are bewildered. Inadvertently speaking in a manner that blames the mother in such situations only adds iatrogenic stress. On the other hand, interviewing the patient in a more leisurely manner than necessary, in an attempt to completely understand the patient's psychological status, will not yield good results. At times temperaments seem to be incompatible regardless of what one does. When that happens, it is sometimes better to bring matters to a close in an appropriate manner and refer the patient to another caregiver.

The most important point is that getting the patients to recognize their unconscious scratching in reaction to stress is all that is necessary, and when re-examining the patient it is best either not to touch on such topics at all, or else lightly touch on them and devote one's efforts toward correcting inappropriate responses to stress. To repeat, the important thing is to make the patients aware of the close association between stress and scratching.

Many medical caregivers complain that they wish to talk with patients in a relaxed manner, but that they don't have time, and there do seem to be circumstances in which practicing physicians, in particular, cannot very well spend

sufficient time with each individual patient. In such situations, it is necessary to make some adjustments, such as by gradually deepening the attentive listening over several sessions or taking some other time to listen to the patient in a more relaxed manner.

In terms of medical fees for these clinical services, while there is a notion that it might be all right to apply special additions, e.g., when more than 30 minutes are required, for psychosomatic therapy (70 points) in the outpatient clinic, psychosomatic therapy should essentially be performed by physicians who have been especially trained for it. The attentive listening described here should be included in the basic medical service, and I should like to think that it is covered by the dermatology specially-designated-disease guidance and management fee (III) (50 points). Moreover, medical care that includes psychosomatic medicine has become routine, and I hope that the number of points for the dermatology specially-designated-disease guidance and management fee (III) for atopic dermatitis will be raised to a generally acceptable level not only for guidance regarding topical care but as compensation for the time spent providing psychosomatic care.

This sort of practical backup may also be needed to make psychosomatic care generally available, but the process of providing psychosomatic care before that, perceiving the patient holistically, and considering the optimal treatment methods together with the patient, provides a deep feeling of satisfaction not only to the patients, but also to their physicians as well. Although there are quite a few difficult patients, a different form of growth as a physician as a human being is to be found in not just explaining the disease in the routine way and writing out prescriptions.

Therapeutic Strategy for Atopic Dermatitis

Several vicious cycles, including "itching and scratching", "barrier destruction by scratching and inflammation", and "stress and scratching" must be broken by the two wheels of "appropriate drug therapy" and "psychological care". More specifically, I think that breaking these cycles can be achieved by both appropriately using topical steroids and immunosuppressive drugs to control the itching caused by existing rashes and identifying the psychosocial exacerbating factors the patient harbors by empathetic and receptive attentive listening and applying appropriate measures, i.e., stress coping to deal with them. Doing so results in completely cure of the habitual scratching in a short time in the majority of patients. Moreover, just by becoming aware of the habitual scratching, even patients who have severe psychosocial factors begin to feel that they can improve their condition themselves, and at least the "wild fluctuations" described in relation to stock prices is no longer seen in the patient's skin.

We have encountered many cases in which after becoming aware the patient soon escaped from these multiple troublesome vicious cycles and recovered. It is often difficult to explain how something behaved in leading to a remission, but there is no doubt as to what the first step is. The "psychological care" that had been abandoned up to now may become the greatest task in the medical care of atopic dermatitis in the future.

REFERENCES

1) Takehara, K. *et al.*: Survey of health damage by inadequate treatment for atopic dermatitis. *Nippon Hifuka Gakkai Zasshi* 2000; 110: 1095–1098. (in Japanese)
2) Kawashima, M. *et al.*: Committee for Guidelines for Therapy for Atopic Dermatitis of Japanese Dermatological Association, ed. "Guidelines for Therapy for Atopic Dermatitis". *Nippon Hifuka Gakkai Zasshi* 2000; 110: 1099–1104. (in Japanese)
3) Kobayashi, M.: Assessment of scratching by atopic dermatitis patients. *Nippon Hifuka*

Gakkai Zasshi 2000; 110: 275–282. (in Japanese)
4) Higaki, Y. *et al.*: The role of psychological stress in severe atopic dermatitis: A consultation-liaison psychoanalytic and clinical approach. *Nippon Hifuka Gakkai Zasshi* 2000; 110: 27–34. (in Japanese)
5) Kusama, M. *et al.*: Evaluation of the psychosocial aggravating factors in adult type atopic dermatitis and its reflection to the treatment. *Rinsho Hifuka* 2002; 56: 195–198. (in Japanese)
6) Okuno, H. *et al.*: Study of psychosocial factors in adult patients with atopic dermatitis (First report): Study of the relationship between pruritus, scratching, and psychological factors. *Nippon Hifuka Gakkai Zasshi* 2000; 110: 837–844. (in Japanese)

Gene Therapy for Peripheral Arterial Occlusive Diseases (PAOD)

JMAJ 45(11): 496–498, 2002

Ryuichi MORISHITA* and Toshio OGIHARA**

*Associate Professor and **Professor, Department of Geriatric Medicine, Osaka University

Key words: Gene therapy; Vascularization; Arteriosclerosis obliterans; HGF; Decoy

Introduction

The incidence of ischemic heart disease and arteriosclerosis obliterans, basically caused by atherosclerosis, is rising with the Westernization of eating habits and the aging of society. Though treatments with advanced drugs and such devices as stents have been developed, there are still many patients who must undergo lower-limb amputations in existing treatments, and post-angioplastial restenosis remains a major problem. Attention has been focused in recent years on the possibilities of gene therapy for these vascular diseases. Gene therapy got its start as a treatment for such congenital diseases as adenosine diaminase (ADA) deficit and has been spreading as a treatment for cardiovascular diseases and multifactor diseases. Therapeutic angiogenesis therapy using VEGF (vascular endothelial growth factor) gene is already being performed in Europe and North America for arteriosclerosis obliterans and ischemic heart disease, and it is reported that their effectiveness exceeds expectations.

Therapeutic Angiogenesis and Their Practice

Endothelial cell growth factors such as VEGF play an extremely important role and are placed at the center of therapeutic aging. Gene therapy for ischemic heart disease and chronic arteriosclerosis obliterans using VEGF genes has already begun in the United States led by Isner *et al.*[1] at Tufts University, and has shown favorable results. They are introducing VEGF genes into muscle in plasmid form by means of intramuscular injection without using virus or other vectors. (Fig. 1)

Rabbit lower-limb ischemic models showed that the intramuscular administration of VEGF or other endothelial cell growth factor plasmid DNA results in the production of vascularization factor and regeneration of blood vessels. Isner *et al.* administered intramuscular injections of VEGF gene plasmid to the lower limbs of arteriosclerosis obliterans patients and reported marked improvement in blood flow. They observed marked increases in ABI (ankle brachial index) and TPI (toe pressure index)

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 126, No. 12, 2001, pages 1692–1693).

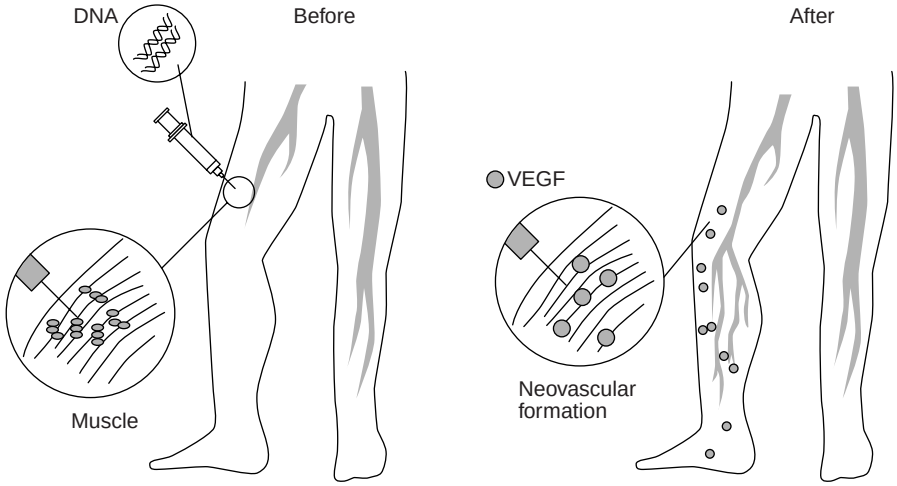


Fig. 1 Therapeutic angiogenesis for arteriosclerosis obliterans and Buerger disease

and improvement of intractable ulcers, indicating the effectiveness of the treatment for severe ischemic limbs, for which conventional treatments have been inadequate.

We demonstrated that an HGF (hepatocyte growth factor) discovered in Japan had a potent angiogenic action[2] and began in June 2001 clinical studies (TREAT-HGF) using HGF genes to treat arteriosclerosis obliterans and Buerger disease. The subjects were patients with arteriosclerosis obliterans or Buerger disease who had pains at rest or ischemic ulcers and necrosis. We injected HGF gene plasmid into morbid limb muscle at four locations, preceded by administration of a preliminary dose and examination for side effects, whereupon we administered the therapeutic dose if no problems appeared. We have currently performed this therapy on six subjects, and observed increased ABI, improved pain, and improved ulcers. The gene therapy clinical studies review committee reported that there was no problem of safety in this therapy.

Since it remains difficult to perform viral gene transfer in clinical practice while the safety of virus vectors is yet to be established, at the present stage muscle tissue seems most appropriate to gene therapy in which genes are introduced in a plasmid form. Since VEGF and HGF are secretory proteins, the genes need not be introduced into all cells and it is possible to raise local concentrations with only partial introductions.

Isner *et al.* are also injecting VEGF genes directly into the myocardium of angina pectoris patients not adaptive to PTCA or CABG, and examining them for ischemic improvement from vascularization. They reported that the number of nitroglycerin dosages fell dramatically for each patient after gene therapy and that angiographic observations showed marked vascularization in each patient resulting from VEGF transgenesis. With SPECT they also observed an expansion of the normal blood-flow region and a decrease in the area of deficiency, indicating the utility of this treatment for ischemic heart disease.[3]

Treatment for Post-Vasodilation Restenosis

A variety of drugs, primarily antiplatelets, have been tried to treat restenosis arising after transcutaneous vasodilation, but none has gained a consensus that it is effective. We have introduced a duplex nucleic acid compound (nucleic-acid-based therapeutic E2F decoy) that acts as a decoy on the transcription control

element E2F binding arrays at promoter regions that are essential to the expression of regulator genes for the cell cycle of smooth muscle into smooth muscle cells in order to prevent the proliferation of smooth muscle cells, and have reported that it is possible to control neointimal growth in rat and pig models of restenosis.[4)]

In April 2000 we began clinical studies (J-PRAS) based on these results of treatments for post-vasodilation and post-stent restenosis with E2F decoy. The E2F decoy is applied to the hydrogel polymer coated on the surface of the vasodilatory catheter and administered after vasodilation. As of February 2002 we have performed five procedures and have observed no acute toxicity, nor any clear side effects in hematological or other examination. So far we have not observed any restenosis but in the future will add to the number of cases and examine the effects of the treatment.

On the other hand, Dzau *et al.* confirmed the effectiveness of the E2F decoy in graft models and in 1996 gained FDA approval for clinical studies of the E2F decoy. *Ex vivo* administration of the decoy to the vein grafts of patients improved the graft occlusion rate of 75% to 25%, confirming the utility of the E2F decoy. Phase III clinical trials are currently underway in the United States, and the decoy is scheduled to go on sale in 2003.

Conclusion

The clinical application of gene therapy for arteriosclerosis obliterans has only just begun in Japan on the basis of research conducted in the past few years and its effectiveness remains under investigation, but it is likely that genetic drugs will find a place in everyday medical examination and treatment in the future. We will be fortunate to be able, with new treatments, to enhance the quality of life of the patients with severe vascular diseases that had only palliative treatments up to now.

REFERENCES

1) Baumgartner, I., Pieczek, A., Isner, J.M. *et al.*: *Circulation* 1998; 97: 1114–1123.
2) Taniyama, Y., Morishita, R., Ogihara, T. *et al.*: *Gene Ther* 2001; 8: 181–189.
3) Losordo, D.W., Vale, P.R., Isner, J.M. *et al.*: *Circulation* 1998; 98: 2800–2804.
4) Morishita, R., Gibbons, G.H., Ellison, K.E. *et al.*: *Proc Natl Acad Sci USA* 1995; 92: 5855–5859.
5) Mann, M.J., Whittemore, A.D., Dzau, V.J. *et al.*: *Lancet* 1999; 30: 1493–1498.