

JMAJ

Japan Medical Association Journal

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Karoshi (Death from Overwork) from a Medical Point of View

JMAJ 47(5): 205–210, 2004

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Abstract: *Karoshi* (death from overwork) is a sociological term used for cases in which an employee who develops cerebrovascular and/or ischemic heart disease, or the family of an employee who dies from such, believes that the disease or the death was triggered or induced by fatigue from overwork, claims that the occurrence of the disease or the death satisfies the definition of prescribed occupational diseases included in the compensation system for employees, and demands payment from the Workmen's Accident Compensation Insurance. The term was used for the first time around 1980 and has, ever since, been actively taken up by the mass media. The administrative measures to handle this condition are summarized in this article. From a medical point of view, fatigue cannot be regarded as a direct cause of cerebrovascular and/or ischemic heart disease. Moreover, no specific pathological changes or tissue damage specifically attributable to fatigue have been identified. Thus, the concept of *karoshi* does not have a firm medical basis. In the court of administrative litigation, the focus of argument is more likely to be the cause of the disease, the quality and degree of fatigue resulting from overwork, or the quality and degree of the underlying disease that the worker already had. *Karoshi* then is a condition that should not exist, and for its prevention, the administrative authority, employers, and employees must make even greater efforts.

Key words: *Karoshi*; Workers' compensation; Social problem; Cerebrovascular diseases; Ischemic heart diseases

Concept of *Karoshi*

The term "*Karoshi* (death from overwork)" is typically used for the following situation. An employee exposed to harsh work conditions,

such as long hours of work, work involving excessive psychological stress and/or work in unpleasant environments, accumulates fatigue developing into a state of overfatigue, and dies of cerebrovascular disease such as cerebral

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 6, 2002, pages 858–861). The Japanese text is a transcript of a lecture originally aired on May 20, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

hemorrhage, subarachnoid hemorrhage and cerebral infarction, or ischemic heart disease such as angina pectoris and myocardial infarction. The family of the employee claims that the death is due to overwork and that it falls under the definition of prescribed occupational diseases included in the compensation system for employees, and demands payment of the Workmen's Accident Compensation Insurance.^{1,2)} The term was first used around 1980, and ever since, has been actively taken up by the mass media, including the print and television media. Now, the word is globally recognized. Recently, a new term, "*karojisatsu* (suicide from overwork)," has also come to be used to refer to suicides resulting from overwork.

Measures Taken by the Japanese Government and the Society to Handle *Karoshi*

In Japan, the law prescribes that "when an employee sustains injury or develops a disease while engaged in work, his or her employer must ensure that he/she gets necessary treatment, and must bear the expenses for necessary treatment" (Article 75 of the Labor Standards Law). This benefit is provided when situations necessitating compensation (workers' compensation) occur. "Prescribed occupational diseases" are listed in Attachment 1-2 of Article 35 of the Enforcement Regulations for the Labor Standards Law. Paragraph 9 mentions "other diseases that are obviously attributable to work."

The procedure by which the Labor Standards Inspection Office that receives a claim for provision of compensation to an employee judges whether the disease for which the claim is being made is truly attributable to work is referred to as "recognition of workers' compensation."

As is well known, cerebrovascular disease and ischemic heart disease (hereafter referred to as cerebral and/or cardiac disease) frequently develop in the general population at large, and not only in employees. No particular increase

in the prevalence of these diseases among employees engaged in specific occupations has been reported. Thus, they are lifestyle-related diseases and not related to any particular occupation or work. However, the Labor Standard Bureau, the Ministry of Labor of Japan made the decision to recognize these diseases as prescribed occupational diseases for the first time in 1961 in the special cases described below.³⁾

In 1961, the administration defined the conditions under which cerebral and/or cardiac disease must be recognized as prescribed occupational diseases as follows: "a suddenly occurring unusual event associated with work for which the time and place of occurrence can be clearly identified, or a situation where, before the occurrence of the disease, the worker had been under excessive psychological or physical stress as a result of being engaged in work under particularly harsh conditions in terms of quality or quantity of work." Thus, the psychological or physical stress resulting from being exposed to particularly harsh work conditions was regarded as a "workers' accident." In the past, only the occurrence of cerebral and/or cardiac disease, or death from such disease, following an unpredictable, sudden, non-ordinary incident at the workplace was recognized as a prescribed occupational disease. An example would be a case where, in the event of a fire at the workplace, an employee engaged in the duty of carrying out important articles develops an acute cerebral and/or cardiac event, or dies from such an event. The law at the time stated that the "outcome of a mere accumulation of fatigue without any accident, cannot be recognized as a prescribed occupational disease or exacerbation of such disease."

In the amendment to the criteria for recognizing cerebral and/or cardiac diseases as prescribed occupational diseases in 1987, the expression, "over-workload," was used in place of "workers' accident," and "overwork during the one week immediately before the occurrence of cerebral and/or cardiac disease/death or an abnormal incident related to work" was

adopted as the basis for its recognition.³⁾ In other words, the working conditions during the one week immediately prior to the occurrence of one of the aforementioned events was taken into consideration in judging the association between disease/death and work. Overworkload was defined as a “workload that is known from medical experience to exacerbate vascular lesions underlying cerebral and/or cardiac disease more suddenly and more dramatically than would be expected in the natural course of events.”

An amendment in 1995 prescribed that “when an employee was engaged in considerable overwork within the one week immediately prior to the occurrence of disease/death, the workload that he/she was exposed to even earlier than the one week immediately prior to the occurrence of the event should also be taken into consideration.”⁴⁾

In an amendment made in 1996, while “sudden death from idiopathic arrhythmia” was also added as an event that may be related to excessive work, the basic tenet of placing importance in the working conditions immediately before the occurrence of an event for making a judgment was not changed. In 2000, criteria for the “recognition of workers’ compensation for psychological disorders related to work, etc.,” including those for the recognition of “suicide resulting from overwork” were newly established.⁵⁾

In 2001, on the basis of the report of a Special Committee⁶⁾ that pointed out that long-term accumulation of fatigue may influence the development of cerebral and/or cardiac disease, and precisely examined the limits of normal workload, the appropriateness of the long-held belief that over-workload in the period immediately prior to the occurrence of disease/death can directly influence the event was ratified, and the following statement was added: “since long-term accumulation of fatigue may influence the development of cerebral and/or cardiac disease, the working conditions during the 6 months prior to the development of such

disease should be specifically and objectively evaluated to determine whether the workload was excessive.”

This chronological review gives the impression that the criteria adopted by the administration for recognizing so-called *karoshi* have been influenced by trends in public opinion and the mass media, as well as the judgment of the court (judiciary), and that the hurdles to granting a judgment of *karoshi* have been gradually alleviated.

Considering these governmental (administrative) policies, the background behind the emergence of the term *karoshi* is probably as follows. An employee or his family insists that the sudden occurrence of cerebral and/or cardiac disease or death from such a disease is due to exposure of the employee to harsh working conditions, demands recognition of the disease as a prescribed occupational disease, and claims payment of workers’ compensation insurance, but the Labor Standards Inspection Office, prefectural labor insurance inspector and the Labor Insurance Appeal Committee all turn down the claim. In such cases, the family, not satisfied with the decision, may appeal to the court (administrative litigation) demanding retraction of the decision. The word, “*karoshi*,” has probably come to be used in the judicial setting during the process of repeated legal disputes against the administration that consistently refused to recognize cerebral and/or cardiac disease as prescribed occupational diseases.

***Karoshi* from a Medical Point of View**

In this section, *karoshi* is discussed from the point of view of a pathologist. Pathology is an approach to explore disease etiology and its pathogenesis, based on the concept that physical deterioration is always associated with morphological changes, and that morphological changes are the bases of functional abnormalities of the body.

Even before the era of Hippocrates (about 460 to 375 B.C.), who is referred to as the

“Father of medicine,” medicine had started as the study of treatment. Pathology, as a science starting from systematic anatomical observation of human body, is believed to have been started by Vesalius (1514–1564). Morgani (1682 to 1771) collected his experiences of morbid anatomy over many years, and published the world’s first book on pathological anatomy entitled “Anatomical study: the localization and cause of disease” (1761). Thus, the concept of “organ pathology” in relation to disease was established. This concept still serves as the mainstay of modern pathologic anatomy. Subsequently, Rokitansky (1804 to 1878), who conducted pathologic-anatomical examination of 30,000 cadavers, established the basic methodology of modern pathology. Virchow (1821 to 1902) published the book “Cellular Pathology” and insisted that all diseases are based on cellular alterations. The fields of microbiology, immunology, and molecular biology appeared in such historical context, and studies in these and related fields have advanced. Thus, characteristic morphological changes and functional abnormalities have come to be described for each known disease. It must be emphasized that most of the concepts regarding diseases known today are based on morbid anatomical and histopathological findings.

Let us look at *karoshi* from this point of view. *Karoshi* is understood as cerebral and/or cardiac disease, or death resulting from cerebral and/or cardiac disease, “triggered” or “induced” by excessive fatigue accumulation due to overwork. However, fatigue has not been shown to be a direct cause of cerebral and/or cardiac disease, and no specific morphological changes specific to fatigue have been identified. In other words, there is no rationale for recognizing *karoshi* as a disease. Thus, the concept of *karoshi* does not stand on firm medical ground. Rather, it should be regarded as a social concept promoted by employees or the families of employees exposed to harsh working conditions that suddenly developed cerebral and/or cardiac disease or died from such disease, and

by the mass media. It no more than symbolizes the wish of the employees or their families, that such disease/death be recognized as a prescribed occupational disease.

Why then Does *Karoshi* Become a Medical Problem?

As already discussed in Chapter II, the workers’ compensation system in Japan prescribes that when there is inherent risk in the work, employees should be compensated for any loss that occurs. In order for a condition to fall under the definition of “other diseases that are obviously attributable to work” in Paragraph 9 of Attachment 1-2 of Article 35 of the Enforcement Regulations for the Labor Standard Law, not only a mere conditional relationship between the work and cerebral and/or cardiac disease, but also a considerable causal relationship should be demonstrated. In order for a considerable causal relationship to be recognized, the risk of onset of the concerned disease needs to be inherent in or associated with the work.

The relationship between the quality and extent of work that an employee is exposed to, and the quality and extent of any underlying disease in the worker can be expressed as shown in Fig. 1.

The first group, represented by the right third of the figure, depicts the cases in which the disease develops in the presence of excessive psychological and physical workload, while there is only mild or no underlying disease. In such cases, the disease can be recognized to be attributable to excessive workload.

The third group, represented by the left third of the figure, depicts cases in which a worker has a serious underlying disease that developed during the course of ordinary routine work. Association of the disease with excessive work can be ruled out.

The second group, represented by the middle third of the figure, is positioned intermediately between the first and third group.

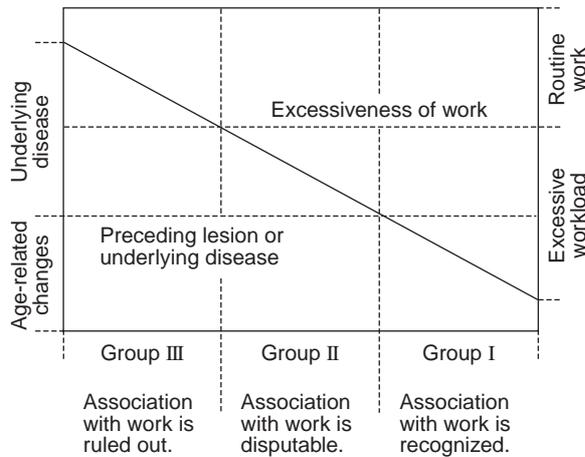


Fig. 1 Diagram illustrating the relationship between excessive workload or excessiveness of work, quality and severity of any underlying disease, and the development of cerebral and/or cardiac disease
A continuous transition can be seen among the groups. The assessment of borderline cases probably poses the greatest disputation.

The presence of cerebral and/or cardiac disease in this group lends itself to dispute as to which is more important; the underlying disease or excessive workload.

Let me compare the relationship using a host-parasite relationship. The first group is equivalent to legally defined communicable diseases that develop when a very highly pathogenic organism enters the body of a healthy person and induces infection. The third group can be compared to an opportunistic infection caused by organisms with little pathogenicity, which is unlikely to induce infections in healthy people, but can cause infections in a person with a markedly reduced immunity level. The second group is comparable with infections occurring in ordinary people caused by microorganisms with ordinary pathogenicity.

At present, numerous factors of overwork are examined in detail and objectively, and are globally taken into consideration when assessing the quality and extent of work to determine whether a subject was exposed to excessive workload. As can be seen from the figure, the quality and severity of the underlying disease in a subject must be inquired at least the same

amount of importance as the workload during such assessment. Therefore, the presence or absence of any risk factors as well as the extent of association of the disease with such risk factors should be carefully evaluated from a medical point of view based on medical evidence, including hereditary predispositions, family history, past history (history of consultation with a doctor and treatment), clinical course of the present illness, and records of periodical health checkups.

The same amount of importance should be attached to the quality and extent of the workload that the employee is exposed to and the quality and extent of the underlying disease when making a judgment on the association between work and the disease, and the final judgment should be made based on such a balanced assessment.

Some recent judicial decisions appear to have been taken based on an inadequate understanding of medicine, without considering the underlying medical condition of the subject. Since the association between the onset of, or death from cerebral and/or cardiac disease and workload is under scrutiny in the *karoshi* issue, reasonable well-grounded discussion of medical problems is essential in the judicial setting as well. From such a point of view, fair opinions given by medical experts will become increasingly important and necessary with respect to cases requiring judgments on *karoshi*.

Future Issues

According to the results of a survey on the health of employees conducted by the Ministry of Health and Welfare in 1997, about 30% of employees suffer from one disease or another. The most common of these included hypertension, gastrointestinal disease, diabetes mellitus and cardiac disease. About 45% of the workers showed great concern and worry regarding their family life, and quite a high percentage had personal worries.⁷⁾ We thus need to pay attention to the tendency toward an increase in

the number of candidates likely to claim compensation for so-called *karoshi*. Moreover, it is impossible to separate the fatigue and stress associated with work from the stress of family life while evaluating the stress and fatigue levels in an individual, especially since stress and fatigue cannot be expressed numerically. Therefore, there are insolvable problems in arriving at a fair judgment in these cases. Prudence is required when extrapolating the results from animal experiments on stress of humans. It should be kept in mind that the general belief regarding fatigue and stress is not necessarily supported by solid evidence. Further advancement of medical research on the subject of fatigue is highly anticipated.

Karoshi is a condition that must not exist. For preventing and decreasing the incidence of *karoshi*, the administrative authority needs to make greater efforts to appropriately guide employees in the direction of health promotion and health management, and employers and employees should cooperate with each other for the establishment of reasonable work hours, to maintain and promote the health of the employees, and to create a pleasant working environment. However, there is a limit to what can be done by administration and employers. Employees must bear in mind that the biggest responsibility for maintaining one's health lies

with each individual. Efforts to prevent *karoshi* are evidently necessary from all standpoints.

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Subarachnoid Hemorrhage and Work

JMAJ 47(5): 211–215, 2004

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Abstract: It is believed that a subarachnoid hemorrhage is caused when a latently developed cerebral aneurysm ruptures; but labor and other physical stresses have little to do with its onset. A cerebral aneurysm is a lesion of a cerebral vessel and sclerosis of a cerebral artery is undoubtedly involved in the rupture, which is the final stage of an aneurysm. In preparing new criteria for approval of reimbursement by workers' compensation insurance, we searched the literature in diverse fields, not only in this country but also overseas, and found that various elements are risk factors in the development of arteriosclerosis. Not only hypertension, but almost all diseases that are regarded to be caused by one's lifestyle are considered to be risk factors. In view of this situation, it is evident by extension that overwork exerts ill effects on lifestyle-related diseases, thus exacerbating the symptoms of these diseases, exaggerating the sclerotic process in the cerebral arteries, and finally resulting in the development of a subarachnoid hemorrhage.

Key words: SAH; Labor; Arteriosclerosis; Lifestyle-related disease; Stress

Introduction

The *Kojien* (a Japanese authoritative dictionary) defines "labor" as: (1) work done through physical effort or by expending energy; (2) activities of a person to create the means for life and manufacturing through an individual's natural efforts; or (3) a specific expression of work dynamics.

When one considers the relationship between a subarachnoid hemorrhage and labor, a common tendency has been to interpret labor by the first definition; and a scenario is projected

in which a subarachnoid hemorrhage develops while a person is engaged in physical labor. However, in the approach taken in setting new criteria for approval in relation to workers' compensation insurance, the concept of labor based on the second definition has been incorporated.

There are a large number of diseases that may cause a subarachnoid hemorrhage, among which a cerebral aneurysm, a rupture of a cerebral arteriovenous malformation, and a hypertensive cerebral hemorrhage are most typical. In recent years, the incidence and mortality of

This article is a revised English version of a paper originally published in the *Journal of the Japan Medical Association* (Vol. 128, No. 6, 2002, pages 871–874). The Japanese text is a transcript of a lecture originally aired on May 23, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Annual Changes in the Incidence of Rupture of Cerebral Aneurysms in the Rochester Area of the United States (per 100,000 people)

Year	Total incidences of subarachnoid hemorrhages	Subarachnoid hemorrhages due to rupture of cerebral aneurysms
1945–1954	10.3	10.0
1955–1964	11.2	10.9
1965–1974	12.2	10.5
	11.6 persons	10.8 persons

(Philips, *et al.*, 1980)

cerebrovascular disorders have been declining but those of subarachnoid hemorrhages have been exceptions. According to a survey conducted in the United States (Table 1), the annual incidence of subarachnoid hemorrhages between 1945 and 1974 was 11.6 cases per 100,000 people. Among these, 10.8 (over 90%) suffered from a cerebral aneurysm rupture.

In this study, the focus will be on the subarachnoid hemorrhage caused by the rupture of a cerebral aneurysm. In addition, the cause for this rupture and relationship with work are discussed.

The Cause of Cerebral Aneurysm Development

There is a theory supporting a congenital origin and another that attaches importance to the effects exerted following birth. Of these two, the former has been regarded as a more prevalent cause. An artery is composed of three sequential layers — the intima, tunica media, and adventitia. The tunica media is composed of strong tissue that supports blood vessels. Some individuals lack this layer. A vascular section that lacks the tunica media is vulnerable to the effects of pressure; and if this happens to be at a vascular bifurcation, it has been said that the pressure exerted on the lesion over the years results in localized vascular bulging and the development of an aneurysm. This absence of the tunica media in a vascular

bifurcation is observed in 80%: yet actual cerebral aneurysms occur in only about 2% of the population. Therefore, it is believed that a cerebral aneurysm occurs as a result of the agenesis of the tunica media combined with other factors.

An understanding of this etiological theory takes on great importance when one considers the relationship between work and a subarachnoid hemorrhage. As discussed later in this study, a subarachnoid hemorrhage occurs during actual work in less than 20% of the cases. However, latent factors that develop as a result of labor over the years constitute dominant causes for the development of a cerebral aneurysm.

To investigate the causes of cerebral aneurysms, induction of the disease has been attempted in experimental animals. Typical methods of production of these experimental aneurysms include: a venous patch grafting in an artery, injection of nitrogen mustard or a hypertonic sodium chloride solution into an arterial wall, and an injection of acrylic resin into the common carotid artery. These experimental aneurysms differ markedly from those seen in clinical patients. In 1987, Hashimoto, *et al.* succeeded in creating a new model, a saccular aneurysm that develops at the bifurcation of the major artery at the vertebrobasilar region, which closely resembled the cerebral aneurysm encountered in clinical practice. Its histological features — the disappearance of the internal

Table 2 States Associated with the Development of a Subarachnoid Hemorrhage

Condition	No. of cases	%
While asleep	46	6
Normal state	187	25
When rising or in a prone position	176	24
Defecation or urination	135	18
Under mental stress	82	11
Cooking or washing	63	8
While bathing	52	7
Coughing	4	0.5
Trauma	3	0.4
Sexual intercourse	1	0.1
Total	749	100%

(Komatsu, *et al.*, 1978)

Table 3 States Associated with the Development of a Subarachnoid Hemorrhage

Condition	No. of cases	%
During rest or sleep	59	11.8
In normal state	172	34.4
Under stress or tension	214	42.8
Defecation or urination	38	7.6
Sexual intercourse	32	6.4
Heavy labor	28	5.6
When rising	26	5.2
In a prone position	24	4.8
Exercise or physical training	19	3.8
Cycling	14	2.8
Lifting a heavy load	12	2.4
Under mental strain	12	2.4
While running	7	1.4

(Schievink, *et al.*, 1989)

elastic membrane and tunica media at the entry to the aneurysm and fibrous connecting tissue composition of the aneurysm itself — were also identical to those of clinical lesions. The process of producing this experimental cerebral aneurysm suggested that hemodynamic changes, hypertension, and fragility of the vascular wall contribute significantly to the development of cerebral aneurysms.

Cause of Cerebral Aneurysm Ruptures

As references, the 1978 data from Tohoku University (Table 2) are often quoted, representing the Japanese studies; and the 1989 data from the University of Amsterdam (Table 3) are cited as typical overseas studies. In the former source, a certain stress condition triggers the subarachnoid hemorrhage in about 70%; but according to the latter, it is lower, at about 40%.

In examining in further detail the state when subarachnoid hemorrhages are likely to occur, Tohoku University reported that only 6% of patients developed the condition when they were asleep, while all others experienced the onset while they were fully awake. Among the

latter, the most common physical activities blamed for the incident were a normal state (25%), a flexing posture of the truncal region (24%), followed by defecation or urination (18%), mental stress (11%), cooking or washing (8%), and bathing (7%).

According to the study by the University of Amsterdam, a subarachnoid hemorrhage occurred in 12% during rest or sleep, 35% while in a normal state, and 43% under some form of stress or strain. Forms of stress or strain contributing to this 43% was: 8% during defecation or urination; 6% during sexual intercourse; 6% during heavy labor; 5% when rising; 5% with their heads down; 4% during exercise; 2% while lifting a heavy load; and 2% under mental stress.

The report by Tohoku University did not give exact statistics on the “development of subarachnoid hemorrhages during labor” but it was implied that bending motions and various psychological tension was involved. In the report by the University of Amsterdam, it appears that heavy labor and various other movements are implicated.

A group at the Tokyo Women’s Medical University conducted a detailed study on the

onset of subarachnoid hemorrhages while the patients were at work. The etiologies for development of subarachnoid hemorrhages were analyzed and its relationship to labor was investigated on 411 cases of a subarachnoid hemorrhage. Subsequently, the group found two peaks for the onset: one was at 7:00 A.M. and the other between 4:00 and 5:00 P.M. Among the patients who experienced the onset of a subarachnoid hemorrhage, 15.1% (the highest percentage) were during work, followed by during rest (12.9%), during sleep (9.5%), while engaged in housework (9%), and during excretion (8.8%).

Next, the work was divided into physical labor (in manufacturing or construction, the actual work being performed in a factory or on-site) and deskwork in a business office. The incidence of a subarachnoid hemorrhage was 2.4% for the former, and 12.7% for the latter.

Next, the work was classified into 5 types — office work (excluding managerial duties), management, physical labor, housework with no outside employment or unemployed, and other. The incidence was noted in 81, 43, 30, 165, and 92 cases, respectively.

The 92 cases classified as “others” were subdivided by specific occupations, such as managing a retail establishment (22 cases); teaching (13); driving automobiles professionally (6); and nursing (3).

Among the 411 cases examined by the group cited above, the circumstances of the activities when the hemorrhage developed were known with 366 patients (159 men and 207 women). The activities implicated in the onset were divided into 2 groups — work and other — and the possible impact of work on onset was investigated. For both men and women, there was a significant difference in the type of occupation ($P < 0.01$) when the incident occurred during work and that associated with other activities were compared. Among men, the incidence was higher during work (clerical work, but not managerial work in an office or physical labor) compared with that associated with other ac-

tivities. The incidence was lower among those in managerial positions, housewives, and the unemployed.

Actual Example

A leading Supreme Court case, which formed the basis for the new approval criteria prepared by the Ministry of Health, Labour and Welfare, and issued in December 2001, is presented below.

A 54-year-old male worker had been assigned to work at a branch office of company T by an organization that dispatches professional automobile drivers. He was assigned to chauffeur for the head of the branch office in 1973. Around 5 o'clock in the morning on May 11, 1984, he left the parking lot near his home and shortly thereafter, he suffered a subarachnoid hemorrhage. The nature of his work — a personal driver for the manager of the branch office — was associated with certain psychological stress. In addition, his work schedule, which had to be coordinated with that of his boss, was highly irregular, often lasting from early in the morning until late at night. This work assignment ran from at least January 1983 through May 11th of the following year when the subject experienced the onset. Thus, it was clear that the patient was under a considerable amount of physical and psychological stress stemming from his work, which in turn caused chronic fatigue.

Under the conditions described above, the patient succumbed to a subarachnoid hemorrhage. The Supreme Court's verdict stated “This court believes that the hemorrhagic lesion of a cerebral aneurysm was exacerbated by chronic hypertension and arteriosclerosis. It is reasonable to conclude that in the cause of the current catastrophe, the background diseases were exacerbated beyond their natural course through an excessive mental and physical overload related to his work. A cause-effect relationship between the nature of the work and the patient's medical condition is believed to exist.”

Conclusion

The incidence of the so-called “lifestyle-related diseases” has recently increased and its control has been urgently desired. The most likely victims of these diseases, those in their 40s and 50s, serve as the nucleus of the work force, and hence from the viewpoint of industrial health, it is considered important to focus on these conditions. A serious problem has surfaced as a consequence of the traditional long working hours and work-centered lifestyle in this country called “*Karoshi* (death from overwork)”, which is defined as “a process in which, triggered by an excessive workload, pre-existing diseases — such as hypertension and arteriosclerosis — are exacerbated to develop cerebrovascular disorders, ischemic heart disease, and acute heart failure, culminating in permanent disabilities or even death.”

“Arteriosclerosis” has the worst possible effect on vascular lesions such as cerebrovascular and ischemic heart diseases (needless to add, this includes the subarachnoid hemorrhage). In considering risk factors for a subarachnoid hemorrhage due to the rupture of a cerebral aneurysm, arteriosclerosis-related conditions — such as hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity, drinking alcohol, and stress — are regarded to have an adverse effect.

Preventing lifestyle-related diseases appears deceptively simple but it is not necessarily easy for those who work to practice it. Routine health examinations have recently become mandatory for workers. For most of them, lifestyle-related diseases or the risk for such conditions will be easily detected in annual health examinations. Needless to add, no such opportunity

is available to those who are employed by companies that do not offer routine health examinations at the work site or for those who are self-employed. In reality, even when the warning signs for the development of lifestyle-related diseases become evident in a health examination, some neglect to seek medical care under the pretext of a busy work schedule or are unable to alter their lifestyle because of a lack of will power. It is too late if the cerebral aneurysm progresses to a stage immediately before hemorrhaging. In such a late stage, it is highly likely that the slightest irritation will cause a rupture of the cerebral aneurysm and a subarachnoid hemorrhage will result.

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Work and Ischemic Heart Disease

JMAJ 47(5): 216–221, 2004

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Abstract: Recent studies provide convincing evidence that work-related stress contributes significantly to the pathogenesis and onset of ischemic heart disease. Work-related stress is one of the most widely studied chronic life stresses related to ischemic heart disease. Many factors in the work environment have been studied in relation to the development of ischemic heart disease. One model proposed based on studies of tension at work is the “job strain” model, defined by Karasek as jobs with high demand but low decision latitude. Hyperresponsivity of the sympathetic nervous system is manifested by an exaggerated heart rate and blood pressure responses to work-related stress. Like other psychosocial factors, chronic work-related stress appears to have direct pathophysiological effects, including stimulation of the hemodynamic system and neurohumoral arousal. However, the data have indicated the existence of individual differences in responsivity of the sympathetic nervous system. Acute stress triggers myocardial ischemia, promotes arrhythmogenesis, and stimulates platelet function, and in the presence of underlying atherosclerosis, it causes coronary vasoconstriction. Because multiple coronary risk factors, including previously established factors such as hypertension, hypercholesterolemia, and smoking, as well as work-related stress, contribute to the development of ischemic heart disease, worker-specific targeted interventions are necessary.

Key words: Work-related stress; Ischemic heart disease;
Sympathetic nervous system; Psychosocial factors;
Coronary risk factors

Introduction

Ischemic heart disease pursues a course that starts with diffuse intimal thickening of the coronary arteries in adolescence, with symp-

toms developing in the final stage, coronary arteriosclerosis, which progresses through complex interactions between cells over a long period. In addition to genetic constitution, lifestyle and environmental factors affect its onset

This article is a revised English version of a paper originally published in the *Journal of the Japan Medical Association* (Vol. 128, No. 6, 2002, pages 875–879). The Japanese text is a transcript of a lecture originally aired on May 24, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

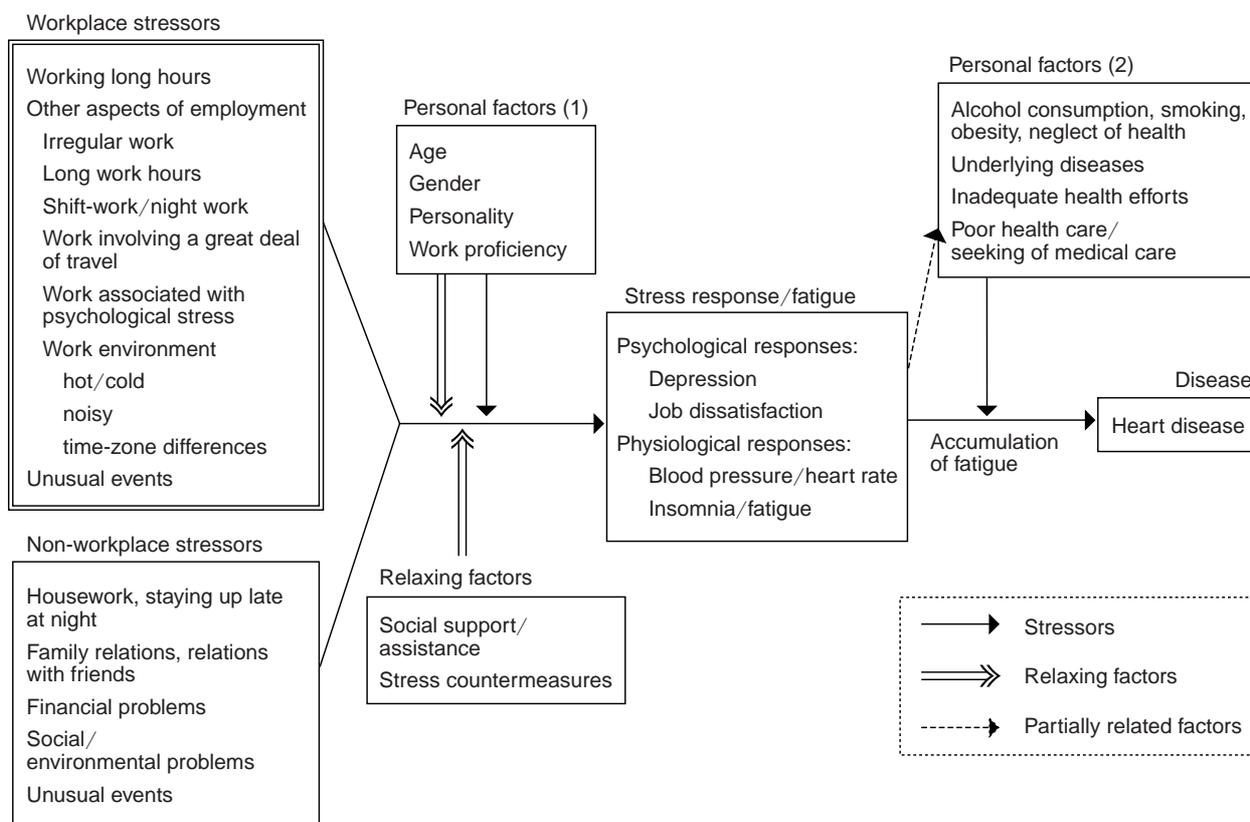


Fig. 1 Work-related stress/relaxation factors and ischemic heart disease
 (Partial revision of the Occupational Stress Model of the United States National Institute of Occupational Safety and Health)
 (Wada, O.: Work and heart disease—Risk factors for “*Karoshi* (death from overwork)”
 and preventive measures. *Quoted from Sangyo Igaku Review* 2002; 4: 186)

and progression. Clinical factors related to the onset and progression of coronary artery disease have been elucidated based on epidemiological studies, including the Framingham Study, and they are referred to by the general term “coronary risk factors”.

Subsequent studies have shown that stress is also a coronary risk factor. Models that consider worker stress based on three types of stressors: 1) workplace stressors, 2) non-workplace stressors, and 3) personal factors, and the opposite, relaxing factors that relieve stress, have been proposed to evaluate worker stress (Fig. 1).¹⁾ In some cases of ischemic heart disease some of these factors, such as amount of work and nature of the work, are thought to play a major role in the onset of the disease as

stressors in the workplace. The social medicine term “*Karoshi* (death from overwork)” has come into widespread use and has attracted the attention of the public. In other cases of ischemic heart disease, in particular, an acute onset occurs in an asymptomatic worker and pursues a course leading to sudden death, giving the family the impression of a disease of the acute onset type. Thus, ischemic heart disease possesses aspects that make it easy to view as a disease associated with industrial accidents.

In this paper I will outline the associations between stress according to type and aspects of work and ischemic heart disease in workers by dividing it into 1) relatively long-term effects and 2) stressors immediately before the onset that act as a trigger.

Table 1 Relative Risk of Multiple Risk Factors for Ischemic Heart Disease
(Model based on the results of the Framingham survey)

Relative risk of multiple risk factors for developing coronary artery disease over a 10- year period (men)

Risk factor	Present (+)/Absent (-)						
	-	+	+	+	+	+	+
Hypertension (systolic pressure \geq 160mmHg)	-	+	+	+	+	+	+
High cholesterol (\geq 250mg/dl)	-	-	+	+	+	+	+
Low HDL-cholesterol (<35 mg/dl)	-	-	-	+	+	+	+
Diabetes	-	-	-	-	+	+	+
Smoking	-	-	-	-	-	+	+
Left ventricular hypertrophy (by ECG)	-	-	-	-	-	-	+
Relative risk	1.0	1.6	1.9	2.7	3.3	4.4	6.6

Onset of Ischemic Heart Disease

1. Definition of ischemic heart disease

In ischemic heart disease the oxygen supply becomes insufficient to meet the demands of the myocardium because of lesions in the coronary arteries, and as a result the myocardium becomes hypoxic (ischemic), and myocardial function is impaired. The term "coronary artery disease" is used when there are lesions in the coronary arteries, but symptoms due to myocardial ischemia or demonstration of myocardial ischemia are not always necessary to make the diagnosis. "Ischemic heart disease" is a diagnostic category based on functional abnormalities that develop as a result of myocardial ischemia, and "coronary artery disease" is a diagnostic term that depends on whether morphological abnormalities are present in the coronary arteries.

2. Progression of atherosclerosis and the onset of ischemic heart disease

"Arteriosclerosis" is a general pathological term used to describe pathological sclerosis and thickening of arterial walls. Based on their pathological characteristics, coronary arteriosclerosis, some cerebral infarctions, and occlusive arteriosclerosis of peripheral arteries are classified under atherosclerosis.

According to pathology studies, it is now

known that diffuse intimal thickening is observed in the coronary arteries in childhood and adolescence, and the thickening is said to be the basis for the development of coronary disease in later years. The lipid-rich plaques of atherosclerotic lesions cause ruptures and fissures, and vessel-obstructing thrombi form and are thought to cause the onset of acute myocardial infarction and sudden cardiac death.

Risk Factors for Arteriosclerosis

1. Outline of coronary risk factors

The chief uncorrectable risk factors are age, gender, and family history. The correctable risk factors include hyperlipidemia, hypertension, smoking, diabetes, and obesity, with three of them, hyperlipidemia, hypertension, and smoking, constituting the greatest risk factors. The impact of the risk factors varies with the pathological type of arteriosclerosis. Hypertension is the greatest risk factor for arteriosclerosis, whereas hyperlipidemia contributes more to atherosclerosis. Recent studies have shown that high serum Lp(a) values, elevated homocysteine values, and high CRP values are also risk factors.

2. Impact of arteriosclerosis risk factors and their evaluation

The impact of arteriosclerosis risk factors in

each individual varies with the strength of the effect of each factor, its duration, timing of its effect, sensitivity and reactivity of the individual, etc. Arteriosclerosis develops when a coronary risk factor acts in addition to a genetic constitution, and when more than one risk factor is present, the risk of developing arteriosclerosis has been found to increase in an additive manner (Table 1).²⁾

Occupational Factors

1. Work time

Based on previous studies, correlations have been reported between long work hours and the prevalence rate of blood pressure elevation and heart disease. The following are suspected of being reasons why long work hours have an impact on cerebrovascular and cardiovascular disease: 1) sleep time is insufficient, and fatigue builds up, 2) decreased breaks and rests during off-work hours and decreased time for leisure activities, 3) the stress imposed by having to marshal mental and physiological functions decreased by fatigue and maintain the constant level demanded by the job when hours are long, and 4) increased time in contact with work-related stressors.

One of these factors, lack of sleep, is thought to increase the responsiveness of the sympathetic nervous system and the prevalence rate of heart disease.³⁾ In a study on the acute effects of short sleep time, significant increases in blood pressure and heart rate were observed at sleep times of 3–4 hours a day. There is also a report claiming a 2.08 times higher mortality rate from ischemic heart disease at sleep times under 4 hours a day than when sleep lasted 7–7.9 hours. In addition, morbidity and mortality from stroke and heart disease have been shown to rise in sleep-deficient states with sleep times under 4–6 hours a day for long periods.³⁾

2. Irregular work hours

Irregular work hours interfere with the sleep-wakefulness rhythm and cause deterioration of

the rhythm of daily living. Moreover, irregular shift-work hours entail the possibility of never being able to take a complete rest. Persons with occupations associated with irregular work hours include transportation workers, such as taxi and truck drivers, guards, and medical personnel on call.

The results of research on shift work and the development of heart disease suggests that the relative risk is 1.2–1.5 times greater, and shift-work hours, frequency, night-work time frame, work intervals, etc., are thought to affect the aggravation by shift work.

However, when shift work is performed according to schedule as routine work or when routine work is in a night-work time frame, the stress experienced can also be considered to fall within the range of the stress in ordinary life. Long work hours and work that involves a great deal of travel may also have an impact on the cardiovascular system.³⁾

3. Work environment

Hot environments are thought to subject the circulatory system to considerable stress, but there have been no data showing a direct association with increased mortality from heart disease, and dehydration may be a factor that triggers its onset. Elevation of blood pressure have been observed during exposure to noise, and there has even been a report describing an association between the onset of ischemic heart disease and noise, but no conclusion has been drawn that it is a risk factor.³⁾

4. Work associated with mental stress

(1) Effect of mental strain on the circulatory system

Changes in the circulatory system due to stress develop as a result of activation of the amygdalo-sympathetic-adrenomedullary system. Its response has been found to consist of blood pressure elevation, increased heart rate, increase in free fatty acids due to an increase in noradrenaline in the blood, and blood glucose elevation. Chronic persistence of this response

is thought to have an effect on the progression of coronary arteriosclerosis mediated by risk factors.⁴⁾ In earlier research blood pressure elevations while at work were reported to be mild. Moreover, while many cohort studies examining work-related stress and the incidence of ischemic heart disease have reported an increased relative risk, other research data have shown no difference, and no consensus has been reached.⁴⁾

Several stress models have been proposed as methods of evaluating the mental stress of work. The job strain model proposed by Karasek and colleagues features a high level of mental strain, low job decision latitude, and little support in society or at work, and a tendency for high levels of stress to develop and an increased relative risk of onset of ischemic heart disease have been shown in so-called "high-demand, low-freedom, low-support" work.^{1,5)}

Generally speaking, there are often large individual differences in response to stress, with the degrees and patterns of response to external factors differing, and medical evaluation of whether acute stage reactions are associated with a significant increase in rate of occurrence of chronic disease, etc., is often difficult.

(2) Occupation/job classification and ischemic heart disease¹⁾

In a study examining the relationship between the onset of stroke and heart diseases and occupation/job classification, associations were reported to have been found with bus and taxi drivers and other motor vehicle drivers, administrative workers, physicians, guards, etc.³⁾ There are also reports that indicate an association between work-related stress and blood pressure elevation and reports that do not. Some studies have shown that systolic blood pressure elevations of 4–12 mmHg and diastolic blood pressure elevations of 2.8–4.3 mmHg while working. However, many of the studies that examined the association between work-related stress and the occurrence of cardiovascular disease over a long period have found low relative risk levels of 1–2.³⁾

5. Personality traits and ischemic heart disease

Associations between personality traits and ischemic heart disease have been investigated by focusing on factors in individuals exposed to stress rather on the stress itself. Freidman and colleagues called the behavior pattern that is susceptible to ischemic heart disease "Type A". Type A behavior is characterized by being short-tempered, aggressive, and emotionally labile, whereas type B is described as not paying much attention to the environment, proceeding at one's own pace, and being easygoing. In an 8-year follow-up survey the incidence rate of ischemic heart disease in the subjects with a type A behavior pattern was reported to be double the rate in the subjects with a type B behavior pattern.

Based on a subsequent study in the United States and Japan an association between "anger" and the onset of ischemic heart disease was reported among subjects with a type A behavior pattern.⁶⁾ Thus, how personality is associated with work-related factors, whether it is an independent factor, and even its chronic effects are unknown. Furthermore, determining whether the onset of ischemic heart disease can be prevented by controlling these factors is a challenge in the future.

6. Short-term overwork as a factor promoting the onset of manifestations of ischemic heart disease

Mental and physical overloading due to encountering unforeseeable circumstances and, in particular, short-term excessive overloading, cause abrupt blood pressure fluctuations, vasoconstriction, etc., with stroke and heart disease sometimes developing, and significant increases in sudden death and acute myocardial infarction as a result of acute stress due to unusual events, earthquakes, etc., have been reported in such cases.⁷⁾ There is a great deal of research evidence indicating that it is reasonable to consider the effect of unusual events that occur between immediately before the onset and one

day before the onset or within one week before the onset. This concept has been incorporated into the approved criteria for death from overwork for some time.

Prevention of Ischemic Heart Disease in Workers

1. Evaluation of work-related factors

Accumulation of fatigue as a result of working for a long period has been demonstrated to affect the cardiovascular system medically as well. However, it is necessary to comprehensively evaluate work-related factors that cause stress based on work hours, irregularity of work hours, fixed work hours, shift work, work environment, and mental strain factors originating from the work. There is also a need for employers and employees to cooperate in efforts to improve working conditions, such as shortening work time, restricting work time outside hours, etc.³⁾

2. Early detection of risk factors for arteriosclerosis by regular health checkups and correcting them

Several risk factors for arteriosclerosis are capable of being corrected by improving one's lifestyle or by treatment. Workers can quit smoking, engage in moderate exercise, consume alcoholic beverages in moderation, and avoid overeating. Cessation of smoking has been shown to reduce the risk of onset of ischemic heart disease to the same level as that of non-smokers beginning immediately after quitting. Continuing to smoke, on the other hand, raises the relative risk to 1.4.

Receiving regular health checkups makes it possible to know whether risk factors are present, e.g., obesity, high blood pressure, hyperlipidemia (hypercholesterolemia, hypo-HDL-cholesterolemia), abnormal glucose tolerance, and the severity of underlying heart disease. If risk factors are detected early, in the mildly abnormal stage, they can be sufficiently cor-

rected by improving one's lifestyle, and it has even been demonstrated that a preventive effect can be obtained by correcting them. These factors generally contribute much more to the onset of ischemic heart disease than work-related factors.

Conclusion

It is impossible to lead a healthy happy life while working without making efforts at self-help. Non-pharmaceutical therapy, such as improvement of lifestyle, improvement of diet, etc., takes priority as a means of preventing ischemic heart disease. The addition of drug therapy must also be considered in patients belonging to high-risk groups.

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Job Stress and Stroke and Coronary Heart Disease

JMAJ 47(5): 222–226, 2004

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Abstract: Repetitive or long-lasting effects of work stressors cause a type of exhaustion referred to as “accumulated fatigue,” that may eventually cause ischemic heart disease or stroke. Among the various work stressors to which people may be exposed, long work hours combined with lack of sleep is a major risk factor in our society. Irregular work hours, shift work, frequent work-related trips, working in a cold or noisy environment, and jet lag are also potent risk factors for workers. In addition, the chronic effects of psychological job strain, which can be conceptualized by the job demand-control-support model, are related to cardiovascular disease. In this model, high job demand and low work control accompanied by low social support at work are the most harmful to health. However, the biomedical mechanisms connecting psychological job strain to cardiovascular disease remain to be fully clarified.

Key words: Job stress; Cardiovascular disease; Long hour work; Job strain

The Concept of Work Stress

The Occupational Stress Model¹⁾ of National Institute of Occupational Safety and Health (NIOSH) is shown in Fig. 1 to facilitate understanding of the concept of work stress and its effect.

Stressors that constantly affect our health exist in all types of work. By interacting with personal factors or non-workplace factors, these work-related stressors induce what are called

‘stress reactions’. There are various stress reactions, including psychological responses (depression and dissatisfaction at work), physiological responses (blood pressure elevation and increased heart rate), and behavioral responses (overeating, overdrinking, smoking, drug use, sickness absence, and accidents). Since the responses are usually acute and transient, health can be restored by taking breaks, resting, sleep, or other adequate approaches.

When exposed to a powerful stressor for a

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 6, 2002, pages 885–888). The Japanese text is a transcript of a lecture originally aired on May 28, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

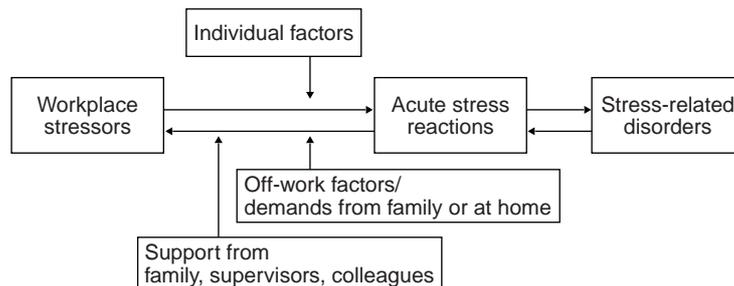


Fig. 1 NIOSH occupational stress model

long period, however, the stress responses increase and become excessive, making it difficult to restore health. This condition is generally called ‘accumulation of fatigue’, and when it persists for a long time, irreversible changes, such as poor physical function and the development of vascular disease, may occur. It may also induce stroke and coronary heart disease in combination with other factors.

Thus, from the standpoint of occupational health, it is important to focus on high-risk, work-related stressors in order to investigate associations between job stress and stroke and coronary heart disease. Stress responses vary with age, gender, personality, behavior and attitude toward work, work skill, underlying diseases, and treatment status. Other factors, such as relationships with supervisors or colleagues at work, regulations and atmosphere in the workplace, daily life outside work, and family relationships and role at home, modify stress responses, and they also need to be examined.

Work-Related Stressors that Increase the Risk of Stroke and Coronary Heart Disease

Based on the results of previous studies and cases reported in Japan, there are three main work stressors related to stroke and coronary heart disease.

The first stressor is the type of work, which is based on the manner in which the work is performed. The second category is physical, chem-

ical, and ergonomic factors in the workplace, and the third is related to the characteristics of the work that are associated with psychological stress.

In this paper, we shall only briefly refer to the first and second categories and focus on the third stressor, the characteristics of work that are associated with psychological stress or mental strain, and their effects.

1. Stressors associated with type of work

One of the major work stressors associated with stroke and coronary heart disease is long working hours. The data in Japan show that the risk of acute myocardial infarction for male workers who work more than 11 hours a day (i.e., approximately 60 hours a month over time) is 2.44 higher than for those who work 7–9 hours a day. Working more than 60 hours a week also increases the risk of cerebrovascular and cardiovascular disease.

The effect of long working hours is closely associated with lack of sleep. Lack of sleep is generally thought to increase the reactivity of the circulatory and sympathetic nervous systems. High angina pectoris and myocardial infarction morbidity among persons getting less than 6 hours sleep a day and 2.08 times higher mortality from ischemic heart disease and cerebrovascular disease among those getting less than 4 hours sleep a day than 7 hours have been reported in some studies.

The entire time spent in the workplace, including nap time, break time, and staying at the

office all night, in addition to actual working hours, also needs to be considered as a problem involved in long working hours. Moreover, some studies have found that when work hours are irregular and the changes of starting time are more than 3 hours, the risk of myocardial infarction is 2.53 times higher than when the change in work hours is less than 1 hour. This indicates that irregular work hours may interfere with sleep-wakefulness rhythm and increase the risk of stroke and coronary heart disease. Some negative research results have been reported for associations between cardiovascular disease and shift work, night work, and early work, but many studies have reported a higher risk of cardiovascular disease associated with changes in shift work, ranging from approximately 1.2 to 1.5 higher.

As to other types of work, work with many business trips increases the risk of stroke and coronary heart disease. Breaks and rests, including sleep time, and recovery from fatigue are keys to prevent such disease, especially in work involving business trips to other countries with large time differences.

2. Physical, chemical, or ergonomic factors in the workplace

Working in a cold environment induces or aggravates ischemic heart disease and cerebrovascular disease. A temperature decrease of 10 degrees Celsius has been found to be associated with a 13% increase in the incidence of attack in coronary artery, an 11% increase in mortality and incidence of coronary artery disease, and a 26% increase in recurrence of attack in coronary artery.

During chronic exposure to noise in a noisy environment (i.e., more than an 80dB noise level), systolic and diastolic pressure elevation, high hypertension morbidity, a 1.2–1.4 higher times relative risk of hypertension due to noise, and a direct association between noise and ischemic heart disease have been observed.

In a comparative study between commercial pilots and a control group, left ventricular hyper-

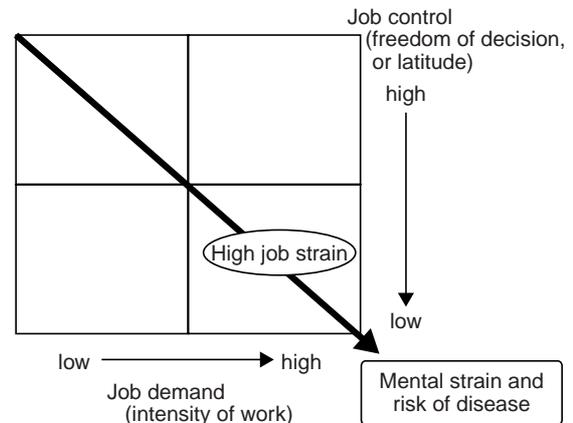


Fig. 2 Job demand-control model

trophy, systolic blood pressure elevation, and high serum cholesterol were more frequently observed in the commercial pilot group, suggesting that shift work system is associated with time difference, and that there is an association between large time difference and stroke and coronary heart disease.

3. Work-related psychological stressors

Some work stressors that induce mental strain have sudden powerful effects, or powerful effects for relatively short periods, and others have repeated effects at work every day over long periods. The latter will be examined in this section.

Psychological stressors in the workplace and their effects have not been fully clarified, because evaluation of work stress is difficult. However, the concept of work stress and evaluation methods have recently become established, and the reliability and validity of the method have been assessed. The number of findings based on these methods has been increasing and we will introduce one of the findings.

Karasek²⁾ proposed a 'job demand-control' model (Fig. 2) to evaluate psychological stressors in the workplace. In this model, work-related psychological stresses occur as the result of the interaction between two factors. One factor is workload and allocation of work, or so-called

'job demand', including the concentration and degree of tension required to do the work, in other words, the intensity of the work. The other factor is latitude, or the freedom of execution and decision at work, or what is referred to as 'job control', under which talents and skills can be demonstrated and improved.

According to Karasek's model, psychological work stress is determined by these two factors and the interaction between them. The combination of a high-level of job demand and low-level of job control, that is, an environment of hard work with little freedom, causes the highest psychological stress and high risk of disease. Study of this 'job demand-control' model has mainly been conducted in Europe, and many findings support the correlation between job stress and cardiovascular disease. This model is now one of the best models for evaluating job stress. Although few results have been reported in Japan, a cohort study showed a significantly lower level of job control among workers who were absent from work due to cardiovascular disease. Support by superiors or colleagues, i.e., human relationships in the workplace, as well as job demand and job control, have been found to greatly modify the effects of job stress. Cardiovascular disease mortality and morbidity are high in groups with severe work stress and little support from supervisors or colleagues, especially among manual workers.

In addition, Johnson *et al.* proposed the 'job demand-control-support' model.³⁾ In this model, the combination of high-level of job demand, low-level of job control, and low social support is associated with the highest level of mental strain and high risk of disease, such as stroke and coronary heart disease. This model is now widely accepted.

Psychological Stress in the Workplace and the Pathogenetic Mechanisms of Stroke and Coronary Heart Disease

The mechanisms by which work-related psy-

chological strain affects the onset of stroke and coronary heart disease have not been identified, but the following have been suggested. First, work-related psychological strain may increase the cardiovascular risk associated with risk factors such as smoking, drinking, blood pressure, obesity, and low physical activity. The overall trend in previous research has shown relatively negative results for an association between job stress and serum lipids, and no consensus has been reached in regard to smoking. Most studies report negative results for an association between job stress and casual blood pressure, but a significant association has been observed with 24-hour blood pressure. There is a difference in blood pressure at home or in a sleep between workers with high job strain and workers with low strain, which suggests that work stress persists even when away from work. Also, it has been suggested that job stress causes depression, leads to low physical activity, and inhibits the improvement of daily habits and coronary risk factors.

Second, job stress may cause coronary arteriosclerosis by other pathophysiological mechanisms. For example, some studies have shown an association between work stress and fibrinogen and HbA_{1c}, which will be clarified in further studies.

Third, at the stage of increasing risk of the onset of disease, psychological stresses in the workplace may trigger the onset of fatal arrhythmia and cardiac infarction. The onset of these diseases is presumably induced by excessive stimulation of the sympathetic nervous system and a delay in recovery from decreased myocardial function. Some studies have shown that working until late at night causes excessive stimulation of the sympathetic nervous system, suppresses the parasympathetic nervous system, and causes blood pressure elevation, especially in hypertensive patients. We expect future studies to identify the effects of work-related psychological stresses in individuals who may have cardiovascular disease.

Conclusion

Here we shall discuss the association between work stress and stroke and coronary heart disease. Type of work, including work hours, work environment, and work-related psychological stressors based on the characteristics of work have been shown to be associated with the occurrence of stroke and coronary heart disease and the course of the disease after the onset. However, the mechanisms of the associations have not been clarified. Additional findings need to be obtained and assessed to determine the association between work-related psychological stressors and the pathogenetic mechanisms of stroke and coronary heart disease in the workplace.

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Classification, Diagnosis, and Treatment of Low Back Pain

JMAJ 47(5): 227–233, 2004

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Abstract: Approaches to the diagnosis and treatment of various kinds of low back pain are described in this paper. As the center and axis of the human body, the low back has to bear a variety of heavy loads during everyday movements, and low back pain has been found to be the most common of various symptoms complained of by the Japanese public in a survey by the Japanese Ministry of Health and Welfare. Thus, correct diagnosis and treatment of the underlying cause of low back pain is essential to maintaining the quality of life of many Japanese. Low back pain caused by fragility fractures in osteoporosis patients has been found to have the most significant impact on mortality among the various kinds of fractures that occur in the elderly. It is concluded that low back pain, a disease of the axis of human body, has a critical influence not only on quality of life, but on the life of the elderly in an aged society.

Key words: Low back pain; Diagnosis; Treatment; Physical findings; Physical therapy

People Want to Lead Their Lives Free of Back Pain

The lower back bears the greatest burden when humans perform a variety of movements and acts as the central axis of the body during our movements in everyday life. Despite this, since the history of humankind walking on two feet is only about 5 million years, a mere 1/30 of the approximately 150-million-year history of mammalian evolution, the structure of the

lower back has not yet adapted to living in the upright position. To cope with this situation, the uterus containing a heavy fetus during pregnancy is located close to the body's center of gravity and pressed up against the lumbar spine to reduce the load, and slight adjustments have been made for the lower back to fulfill its role as the pivot of the body, such as curving forward and inclining toward the center of the trunk to support the upper part of the body.

We have reduced the load on the lower back

This article is a revised English version of a paper originally published in the *Journal of the Japan Medical Association* (Vol. 128, No. 12, 2002, pages 1761–1765). The Japanese text is a transcript of a lecture originally aired on September 2, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

Table 1 List of the Most Common Symptoms Complained of by the Japanese Public (per 1,000 population)

Symptom	All ages	Persons 65 years of age and over
One or more of them	305	530
Low back pain	93	201
Stiff shoulders	91	128
Joint pain in the extremities	54	152
Cough/phlegm	51	81
Fatigue	48	55
Poor vision	47	128
Nasal obstruction	45	36
Itchiness	39	62
Headache	37	50
Eyestrain	36	94
Forgetfulness	34	109

The top 11 symptoms complained of in a survey of 780,000 people in 280,000 households living in 5,240 areas throughout Japan reported in June 2000. (Ministry of Health and Welfare, Faculty of Statistics and Information, ed.: Basic survey of the everyday lives of the Japanese public (1998): Tokyo, 2000.)

in our everyday lives by consigning primary industries that entail bending the body forward, such as tilling fields, to electrical power and petroleum energy. However, a report on the incidence of low back pain among employees in the construction industry based on a survey of 18,535 workers at construction sites (mean age: 39 years) and 7,675 office workers (mean age: 39 years) revealed a rate of 30.1% in the construction workers and 31.3% in the clerical workers, and there was little difference in the incidence of low back pain between them.¹⁾ Despite affecting such a large number of people, the incidence of low back pain rises even higher with age, and approximately 43% of construction workers 55–59 years of age complain of low back pain. Even if the number of primary industry workers decreases in the future, the number of people providing nursing care in the service industries is expected to increase to 300 thousand nationwide, and since about 1/3 of them experience low back pain, it seems valid to conclude that low back pain is a symptom that human beings will find difficult to escape.

Although there seem to be many other symp-

toms that are old foes of the human race, as shown in Table 1, a national survey to identify the most common symptoms complained of by the public revealed low back pain to be the most common complaint, with a rate of 93 persons per 1,000 population, and among persons 65 years of age and older, the rate was 201 persons per 1,000. Although we tend to think of poor vision, forgetfulness, etc., as becoming the most common symptoms as people grow older, the elderly actually complain of low back pain about twice as much as these other symptoms.²⁾ Thus, low back pain troubles many people in all decades of life, and they are hoping for a life free of low back pain.

Classification of Low Back Pain

Low back pain occurs as a result of a variety of causes and pathological conditions, and because it is sometimes difficult to diagnose, there are times when the physician has no other choice than to make a diagnosis of “low back pain”, which simply describes the symptom. However, when examining low back pain patients, as shown in Table 2, an effort must be

Table 2 Diseases Associated with Low Back Pain Classified According to Etiology

Etiology	Disease
Trauma	Lumbar intervertebral disc hernia Muscular/fascial low back pain [acute muscular low back pain (sprained back), chronic muscular low back pain] Low back pain associated with fractures (traumatic vertebral body fractures, fragile vertebral body fractures associated with osteoporosis)
Inflammation	Tuberculous spondylitis Purulent spondylitis Ankylosing spondylitis
Tumors	Spinal metastasis by malignant tumors Multiple myeloma Spinal cord tumors
Degeneration	Spondylosis deformans Intervertebral disc degeneration Intervertebral articular low back pain Lumbar non-spondylolytic spondylolisthesis Ankylosing spinal hyperostosis Lumbar spinal canal stenosis
Abdominal organs	Diseases of the liver, gallbladder, pancreas, etc.
Psychological	Psychogenic low back pain, in hysteria, depression, etc.

made to make a diagnosis according to its etiology based on the history, physical findings, and results of the diagnostic tests, because identifying the etiology is essential to providing appropriate treatment.

1. Low back pain caused by trauma

Acute muscular low back pain (sprained back) occurs when exposure to an external force, such as in a collision with a person or while lifting a heavy object, damages muscles and fascia, while lumbar intervertebral disc herniation occurs when an intervertebral disc collapses and compresses nerves anteriorly, and traumatic vertebral body fractures occur when a vertebral body collapses as a result of a fall, etc. Chronic muscular low back pain develops when repetitive muscle use is performed over and over again, and fragile vertebral body fractures associated with osteoporosis occur when bone fragility progresses and bones collapse even in the absence of exposure to major external force.

2. Low back pain caused by inflammation

Tuberculous spondylitis or purulent spondylitis develops when tubercle bacilli or pyogenic bacteria destroy vertebral bodies or intervertebral discs. If the vertebrae are connected like bamboo, the patient has ankylosing spondylitis, a rheumatic disease that is negative for rheumatoid factor.

3. Low back pain caused by tumors

Malignant tumors, such as lung cancer, stomach cancer, breast cancer, prostate cancer, etc., sometimes metastasize to the lumbar spine, and disseminated metastasis to the lumbar spine is one of the pathological pictures of multiple myeloma. When tumors such as neuromas or angiomas develop in the lumbar cord or lumbar spine, patients experience intense low back pain.

4. Low back pain caused by degeneration

As construction workers advance in age, their incidence of low back pain increases, and the

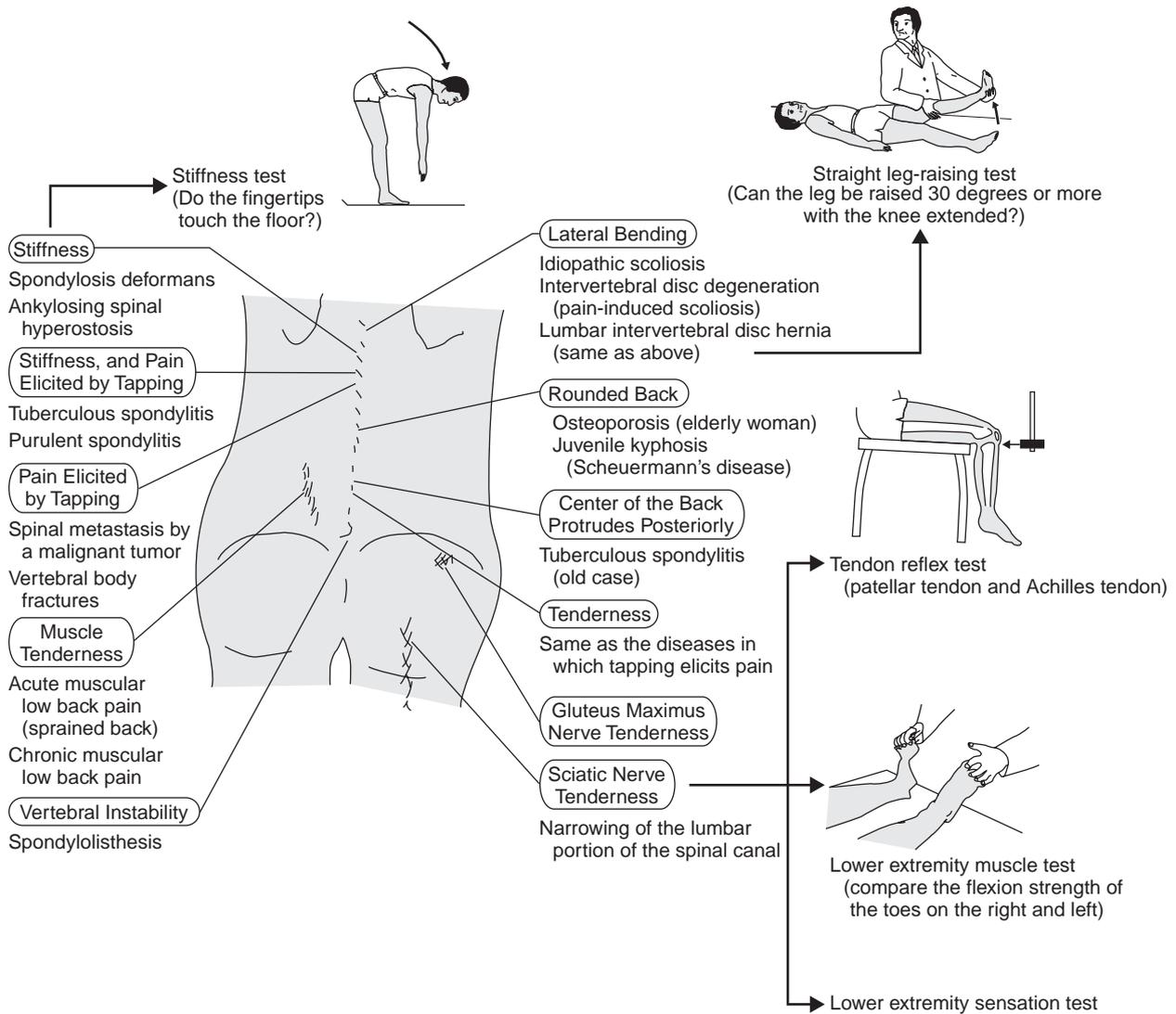


Fig. 1 Methods of diagnosing low back pain by inspection and palpation

increases are attributable to the development of lesions associated with degeneration of the lumbar spine and surrounding tissues. Degeneration leads to the development of spondylosis deformans, lumbar intervertebral disc degeneration, intervertebral articular low back pain, lumbar non-spondylolytic spondylolisthesis, ankylosing spinal hyperostosis, and lumbar spinal stenosis.

5. Low back pain due to other causes

In addition to diseases that arise in the structures that compose the lower back, which is the

pivot of the body, pain arising from diseases of intra-abdominal organs, including the liver, gallbladder, and pancreas, and referred pain are also seen among the diseases that give rise to low back pain. Pain also arises from posterior abdominal organs, including the uterus, ovaries, and urine bladder. The existence of psychogenic pain associated with hysteria and depression must also not be forgotten.

Diagnosis of Low Back Pain

When low back pain has been determined

to be of skeletal origin based on the history, proceed to inspection and palpation of the lower back. The diagnostic methods are shown in Fig. 1. First, inspect for curvature of the spinal column anteriorly, posteriorly, and to the right or left. No curvature to the right or left is seen in normal persons, but when the spinal column is curved laterally and tilted in just one direction, interpret it as representing scoliosis in an effort to avoid pain, and consider lumbar intervertebral disc hernia or intervertebral disc degeneration. If the center of the scoliosis is in the thoracic spine and compensatory scoliosis in the opposite direction in the lumbar spine gives the spine as a whole the shape of the letter "S", consider idiopathic scoliosis. When the lower back protrudes posteriorly in a gentle manner, interpret it as representing kyphosis, and consider Scheuermann's disease (juvenile kyphosis) if the patient is young, and osteoporosis if the patient is an elderly woman. If the posterior protrusion of the lumbar portion of the back is steep, it often represents an old case of tuberculous spondylitis.

A state in which the flexion and extension movements of the spinal column are poor is described as "stiffness", and the spinal column is as rigid as bamboo and exhibits stiffness in spondylosis deformans, ankylosing spinal hyperostosis, and ankylosing spondylitis. Intense low back pain and stiffness of the spinal column occur in the initial stage of tuberculous spondylitis and in purulent spondylitis. In diseases in which pain is elicited by tapping or palpating spinal processes at the center of the posterior of the spinal column, there is spinal metastasis by a malignant tumor or a vertebral body fracture in addition to the above-described spondylitis. When tenderness is elicited in the paravertebral muscles immediately adjacent to the lumbar spine, consider acute muscular low back pain (sprained back), caused by a sudden tear of muscle or fascia in the same area, or chronic muscular low back pain. In lumbar spinal stenosis, tenderness is observed along the ends of the gluteus major nerve in the supero-

Table 3 Principles for Treating Low Back Pain

1. Low back pain originating in abdominal and posterior abdominal organs. Low back pain due to spinal metastases of malignant tumors
Cure the low back pain by treating the underlying disease.
2. Low back pain that can be cured by surgery
Decide whether to perform surgery in the early stage or after monitoring the patient conservatively.
3. Low back pain without indications for surgery
 - a. Rest: Restriction of physical activity, or local rest with a corset, etc.
 - b. Physical therapy: Principally thermotherapy, but also traction
 - c. Exercise therapy: Attempt (1) to increase muscle strength and produce a "natural" corset by means of abdominal and low back muscles, (2) to perform stretch and relaxation exercises, and (3) to increase bone strength by imposing mechanical loads on bones.
 - d. Orthoses: Not just immobilizing the low back, but eliminating pain by correcting kyphosis and scoliosis as much as possible.
 - e. Drug therapy: (1) Curative therapy with antibiotics or antitubercular agents, (2) symptomatic therapy with anti-inflammatory analgesics, and (3) elimination of pain by means of local blocks and nerve blocks.
 - f. Psychotherapy: Counseling for chronic low back pain and psychogenic low back pain.
 - g. Guidance for everyday living: Guidance in regard to inappropriate life styles and work.

lateral area of the buttocks or along the center of the posterior aspect of the thigh. While touching the spinal processes of the lower 3 lumbar vertebrae, have the patient flex and extend the lumbar spine, and palpate the vertebral bodies for instability, in other words, to see whether they slide due to spondylolisthesis.

In addition to examining the lower back, other methods that are useful in making a definitive diagnosis of low back pain are the stiffness test, in which the patient bends forward and the distance between the fingertips and the floor is measured, and the straight leg-raising test, in which the legs are raised with the knees extended in the supine position. Testing sensation, muscle strength, and tendon reflexes in the legs and determining whether paralysis is present in the area supplied by the sciatic nerves are also important from a diagnostic standpoint.

Treatment of Low Back Pain

Because of the diverse etiology of low back pain, there are various methods of treating it, and the principles of treatment are listed in Table 3.

1. Treatment of the causative disease

Treatment of the underlying disease causing the pain is given priority in patients complaining of low back pain originating in abdominal or posterior abdominal organs. Similarly, treatment with anticancer drugs, radiation therapy, etc., must be considered in patients complaining of low back pain who have spinal metastases of malignant tumors or bone lesions produced by multiple myeloma.

2. Surgery

Low back pain that is considered to have indications for surgical treatment includes extension of sciatic nerve paralysis toward the lower extremities, progression of nerve root compression symptoms, and infection caused by *M. tuberculosis* or other bacteria. Care must be taken not to miss the time for surgery while conducting conservative therapy before the operation. The criteria for surgical indications are reduced mobility in everyday life and development of paralysis in lumbar spinal stenosis, and progression of the paralysis in lumbar intervertebral disc hernia. If paralysis develops in a patient with a spinal cord tumor, surgery must be performed without delay.

3. Conservative therapy

Rest is usually advised as the first method of reducing low back pain, without considering surgery. Rest can be approached in two ways, by restricting daily activity and by attempting to achieve local rest by fixing the lower back with a corset, etc.

Among physical therapy modalities, in addition to thermotherapy with hot packs, disposable body warmers, and bathing, pelvic traction by applying traction force to the lumbar spine

is an effective means of physical therapy for lumbar intervertebral disc hernia. Thermotherapy is contraindicated for low back pain caused by inflammation or tumors.

Exercise therapy, such as performing relaxation and stretching exercises to eliminate muscle tension, creating a "natural" corset by abdominal and low back muscle training, and attempting to strengthen bones by imposing mechanical loads on them are useful in treating low back pain.

Scoliosis and kyphosis cannot be completely corrected with orthoses, but they have the advantage of preventing progression and instilling a sense of security.

Drug therapy is available for curative therapy and symptomatic therapy. Local infiltration (trigger point) blocks or nerve blocks with anesthetics also sometimes have a curative effect on low back pain.

Psychological counseling is effective for chronic low back pain and psychogenic pain, and guidance in regard to everyday living should not be forgotten.

Diagnosis and Treatment of Low Back Pain are an Inevitable Part of Medical Care in an Aged Society

Since low back pain is extremely common among the various symptoms and diseases with which clinicians are confronted, uncovering its precise cause and diagnosing and treating it occupies an important position in continuing to maintain the quality of life of elderly patients and in maintaining longevity in the medical care of an aged society. I will now elaborate on these points in regard to osteoporosis, one of the principal diseases responsible for low back pain in the elderly.

The main goal of the treatment of osteoporosis 40 years ago, when there were few alternatives to choose from, was remission of the low back pain. As a result of advances in medical care, the goal of treatment subsequently changed to increasing bone density and

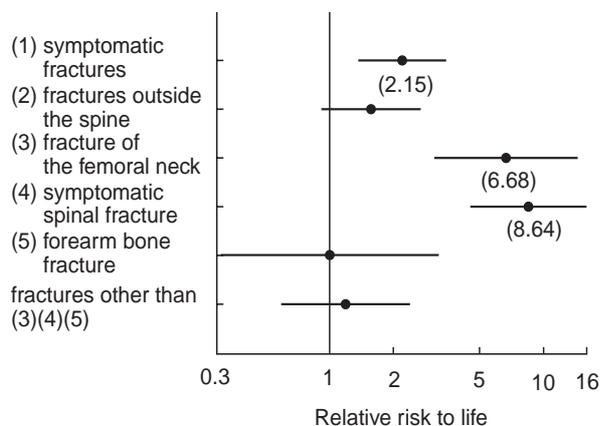


Fig. 2 Relative risk of various bone fractures to the life of elderly patients

Of the various types of bone fractures assessed, vertebral body fractures associated with low back pain posed the highest risk to the life of elderly persons. A total of 6459 women, mean age 69 years, were followed up for an average of 3.8 years. Fractures occurred in 907 of them, and the relationship between the deaths of 122 of them and the fractures was investigated. Relative risks are shown in parentheses. (Quoted from Cauley, J.A. *et al.*: Risk of mortality following clinical fractures. *Osteoporosis Int* 2000; 11: 556–561).

then to lowering the fracture rate, and now attention is being focused on how to reduce femoral neck fractures, which have the most negative impact on the functional prognosis of osteoporosis patients. Accordingly, lumbar compression fractures and kyphosis, as well as the low back pain attributable to them, are being treated as warning signs of leg fractures, and there is a feeling of having become detached from the main targets of diagnosis and treatment. However, when analyzed from the standpoint of the quality of life of the elderly, kyphosis, low back pain, etc., were found to make the elderly tend to become reclusive as a result of psychological factors, such as lowering their body image, causing them to fear falling, etc., and as a result of the instability factor of gait difficulty with festination and their standing posture because of flexion contractures of the knees secondary to kyphosis.³⁾ Because of this, how to reduce vertebral body fractures associated with clinical manifestations in the treatment of osteoporosis has been restored as a parameter for evaluating the efficacy of drugs

for the treatment of osteoporosis.⁴⁾

Numerous large-scale clinical studies have been conducted to investigate the efficacy of drugs for the treatment of osteoporosis, and in one of them 6,459 women with a mean age of 69 years were followed up for an average of 3.8 years.⁵⁾ Fractures occurred in 907 of the 6,459 women, and 122 women died. As shown in Fig. 2, vertebral body fractures, which were manifested by low back pain, etc., posed the highest risk to life among the wide variety of fractures they experienced. There were no differences in amount of exercise, smoking history, morbidity of heart disease, bone mineral density, etc., among patients with different types of fractures, and the largest number died of only vertebral body fractures associated with low back pain. With this point I will conclude by stating that the lower back is the pivot of the body, and the diagnosis and treatment of low back pain rank fairly high.

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Physical Therapy for Low Back Pain

JMAJ 47(5): 234–239, 2004

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Abstract: Physical therapy consists of fixation, thermotherapy, traction, and physical training. The symptomatic therapy is effective for some low back pain, including pain due to metastasis by malignant tumors. Fixation with a corset or wide canvas band reduces muscle pain in the low back region as curative therapy, but reduces the pain caused by tumors or inflammation as symptomatic therapy. Thermotherapy is the most popular form of the 4 types of physical therapy used in medical institutions in Japan. Thermotherapy includes deep heat, such as produced by microwaves and superficial heat, such as produced by hot packs and paraffin baths. Traction other than pelvic traction for lumbar intervertebral disc hernia has recently been losing popularity, because of the prolonged hospital stays required. Physical training is expected to be the most effective method of reducing low back pain. Strengthening low back and abdominal muscles after muscle stretch exercises is effective in reducing low back pain because it has a “natural” corset-like effect that prevents pain.

Key words: Physical therapy; Fixation; Thermotherapy; Traction; Physical Training

Physical Therapy Contributes to Reducing Low Back Pain

Physical therapy, which consists of exercise therapy, such as fixation, thermotherapy, traction, and muscle strengthening, and guidance in regard to everyday activities, contributes to reduction of low back pain in either an auxiliary manner or as the fundamental modality of treatment, depending on the disease. Thus, although we recommend physical therapy, which

is less invasive than drug therapy or surgical therapy, as the treatment of the first choice for low back pain, it is important to determine whether its role is as auxiliary therapy or as the fundamental modality of treatment. A correct diagnosis of the disease responsible for the low back pain is also essential in order to make this distinction.

Five different types of physical therapy for low back pain, and the diseases for which they are indicated, are listed in Table 1. For example,

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 12, 2002, pages 1800–1803). The Japanese text is a transcript of a lecture originally aired on September 5, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

Table 1 Physical Therapy for Low Back Pain

1. Fixation (corset, bleached cloth, etc.)	Acute muscular low back pain (sprained back) Vertebral body compression fractures, invasion of the lumbar spine by bacteria/tumors
2. Thermotherapy (hot pack, microwaves)	Chronic muscular low back pain, intervertebral disc degeneration, spondylosis deformans, ankylosing spinal hyperostosis, non-spondylolytic spondylolisthesis, lumbar spinal canal stenosis, kyphosis secondary to osteoporosis
3. Traction (continuous, intermittent indirect)	Intervertebral disc degeneration, lumbar spinal canal stenosis, and lumbar intervertebral disc hernia
4. Exercise therapy (muscle strengthening, Williams' exercises)	Chronic muscular low back pain, degenerative diseases of the lumbar spine
5. Guidance in everyday living	
a. Bone strengthening:	Low back pain secondary to osteoporosis
b. Muscle rest:	Acute and chronic muscular low back pain
c. Load reduction:	Degenerative diseases of the lumbar spine

methods designed to eliminate pain by fixing the lower back with a corset or wide canvas band in acute muscular low back pain (sprained back) are classified as fundamental therapy, that is, they are expected to lead to regeneration or healing of torn muscles. However, fixation for invasion of the lumbar spine by bacteria or a malignant tumor, as in tuberculous spondylitis or spinal metastasis by a malignant tumor, is only a means of relieving low back pain temporarily. Drug therapy or surgery of the underlying disease is important as curative therapy in both of these diseases, and to the extent that the curative therapy is ineffective, the low back pain fails to resolve. Fixation for vertebral compression fractures corresponds to fundamental therapy, since it is designed to promote bone healing and eliminate pain, but the existence of curative treatment methods that improve bone fragility must not be forgotten. For these reasons, in order to use physical therapy effectively in low back pain, it is important not to

overlook two important diseases that are only very rarely encountered and account for less than 1 in a 1000 low back pain patients: purulent/tuberculous spondylitis and spinal metastasis by malignant tumors.

Guidance in everyday life, which corresponds to physical therapy in the broad sense, is also important. We teach the importance of daily exercise to strengthen the bones in osteoporosis, and the importance of postures that allow rest without imposing a load on the muscles in acute and chronic muscular low back pain, and guide patients accordingly. In addition, as for lumbar spine degeneration, we guide a strategy to decrease load to lumbar spine, and avoid the progression of the degeneration. In addition, in degenerative diseases of the lumbar spine, we guide to reduce the load of the force on the lower back to prevent the progression of the diseases.

Fixation

Fixation of the lower back by means of bleached cloth, corsets, etc., reduces low back pain by 3 actions: (1) limiting the movement of painful muscles, intervertebral joints, intervertebral discs, and fractured vertebral bodies, (2) maintaining good posture so as to reduce the mechanical load on the lower back, and (3) reducing the mechanical load on the lower lumbar spine.

Not only does limiting movement eliminate pain in the muscles, bones, joints, and intervertebral discs that compose the lower back, but it can promote healing of the underlying disease. For example, acute muscular low back pain caused by muscle and fascia tears, vertebral body compression fractures manifested by bone collapse, intervertebral arthropathy manifested by mild inflammation in the joints, intervertebral disc hernia, in which a protruding disc compresses the spinal cord, etc., start to heal as a result of fixation. Methods in which the thorax and the pelvis are fixed rendering the lumbar spine rod-like is effective in limiting

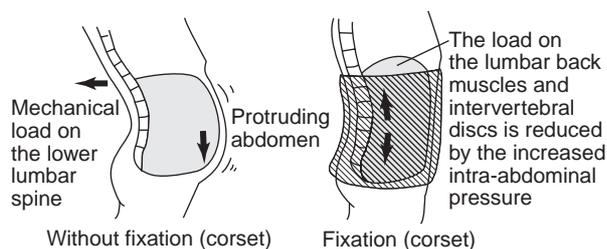


Fig. 1 Lumbar-pain-reducing effect of fixation (quoted from Iwakura, H., *et al.* eds.: Diseases of the trunk and musculoskeletal system, and rehabilitation. Ishiyaku Publishers, Inc., Tokyo, 1985; pp. 133–196.)

the movements of these tissues, and a slightly longer elastic corset than usual (Damen corset) or a Knight corset with a metal bar in its posterior portion are used for this purpose.

The Williams' flexion orthosis is available as a firm corset that has a corrective effect in lessening the anterior curvature of the lumbar spine by means of a metal frame. Although it is said to be suitable for sustaining good posture, in the author's experience the patient compliance rate is poor. By contrast, flexible corsets, which are short, easy-to-remove types sold in pharmacies, have a good compliance rate, and many patients have found them to be effective. The reason is that, as shown in Fig. 1, fixing the lower back and abdomen as though hoops had been slipped onto a barrel make it possible to correct the protrusion of the abdomen and raise intra-abdominal pressure, which reduces the external force on the posterior lumbar muscles and lumbar intervertebral discs.¹⁾

Based on the above, it can be concluded that long, firm corsets are useful as a method of fixation for low back pain when the aim is to achieve bone fusion after vertebral body compression fractures and to relieve intense pain caused by purulent or tuberculous spondylitis, metastases of malignant tumors. However, fixation with relatively short Damen corsets or bleached cloth is adequate for most other forms of low back pain in terms of efficacy, compliance, and comfort.

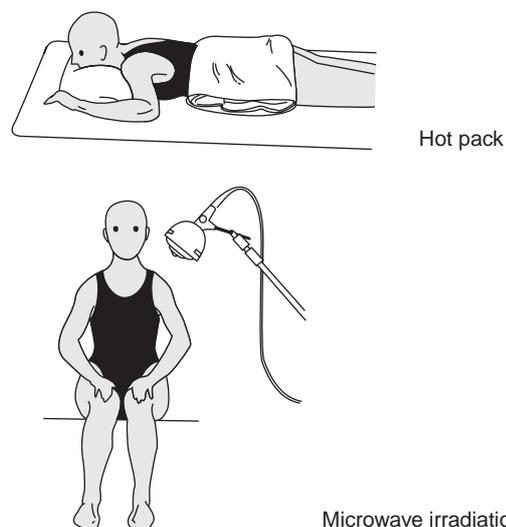


Fig. 2 Thermotherapy by hot pack and microwave therapy
The hot pack is designed to reduce pain by the action of heat on the surface (conduction heat), while microwave therapy is designed to relieve pain by the action of heat deep inside the body (deep heat).
(quoted from Yoshimura, S.: The course of physical therapy in stroke patients. Hayashi, Y. ed.: Rehabilitation Manual. *Journal of the Japan Medical Association* (extra issue) 1994; 112(11): 19)

Thermotherapy

Thermotherapy of low back pain is the most frequently used form of physical therapy performed in medical institutions. Thermotherapy is divided into methods that use surface heat and methods that use deep heat, and other forms of thermotherapy include hydrotherapy in the form of partial baths and whirlpool baths, and hot springs, which have a change-of-climate effect and mental-relaxation effect.

As shown in Fig. 2, there are 3 forms of thermotherapy that use surface heat, a form that uses conduction heat, including hot packs and paraffin baths, a form that uses radiant heat, including infrared rays, and a form that uses convection heat, including hydrotherapy and hot air baths. Methods that involve exposure to microwaves or ultrashort waves, on the other hand, are classified as deep-heat thermotherapy.²⁾ A therapeutic effect begins to occur after 3 to 5 minutes of exposure to their heat, and the maximal effect is obtained after 30

minutes. However, since burns occur when the temperature of the dermis and epidermis is raised to 42°C and heated for several hours, thermotherapy at no more than 45°C for about 30 minutes can be said to be in the safe range (but there are individual differences).

Not only does blood flow in local arterioles and capillaries increase when exposed to heat, but sympathetic vasodilatation occurs in distant areas as well. Local metabolism also accelerates; nerve sensitivity decreases, and the pain threshold rises. The sensitivity of muscle spindles, nerve endings that affect muscle tonus, decreases in response to heat, and muscle spasms are prevented. The extensibility of connective tissue increases, and joint contractures are relieved. The increase in muscle blood flow is also associated with the removal of substances related to fatigue and pain-inducing substances within the muscle. In this way heat has a rapid effect in relieving low back pain.

Thermotherapy is contraindicated for low back pain in the presence of acute inflammation, for example, in active tuberculous spondylitis or purulent spondylitis. Since heat increases the pain in malignant tumors and may increase the size of the tumors, it is also contraindicated in spinal metastasis of malignant tumors. Moreover, burns tend to occur in patients with impaired sensation, and heat exacerbates the swelling when edema is present. When artificial joints or metal inside the body is exposed to deep heat, the heat becomes concentrated and burns tend to occur, and thus deep heat is contraindicated when metal is present in the body.

Traction

Traction is frequently performed in diseases of the cervical spine and for fracture reduction and fixation. However, because of the efficacy of anti-inflammatory analgesics, blocking therapy and the development of surgical procedures that replace it, traction is being used less often to eliminate low back pain. The recent

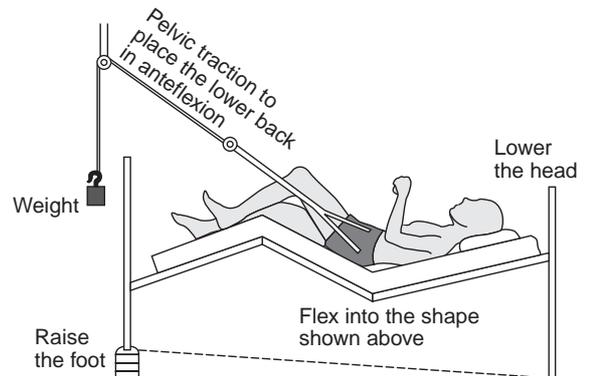


Fig. 3 Traction for lumbar intervertebral disc hernia

trend toward shorter stays in medical institutions can be cited as another reason why traction for low back pain has been replaced by other treatment modalities.

Traction exerts its greatest efficacy against low back pain when used to treat lumbar intervertebral disc hernia. As shown in Fig. 3, a pelvic traction band is usually wrapped around the pelvis with the patient resting in the supine position, and traction is applied by means of a 5–10 kg weight at the foot of the bed. This procedure is effective, because when the lumbar area—pelvis is flexed 20–30 degrees like a craft knife, it acts in a direction that reduces the protruding intervertebral disc back into position. Because of the strong traction toward the foot of the bed, the body imperceptibly slides in that direction, and the weight exerting the traction force may eventually touch the floor. To prevent that from happening, the head of the bed can be lowered slightly and the bottom raised by placing blocks under the legs at the foot of the bed and raising it 10 cm off the floor. When traction is applied in this manner, the symptoms improve within 3–7 days. Resolution of the low back pain is often observed in about 2 weeks, and the traction can be discontinued at that time.

The traction used for lumbar intervertebral disc hernias, called “pelvic traction”, used to be performed for lumbar spinal canal stenosis, which was diagnosed as sciatica, and was effec-

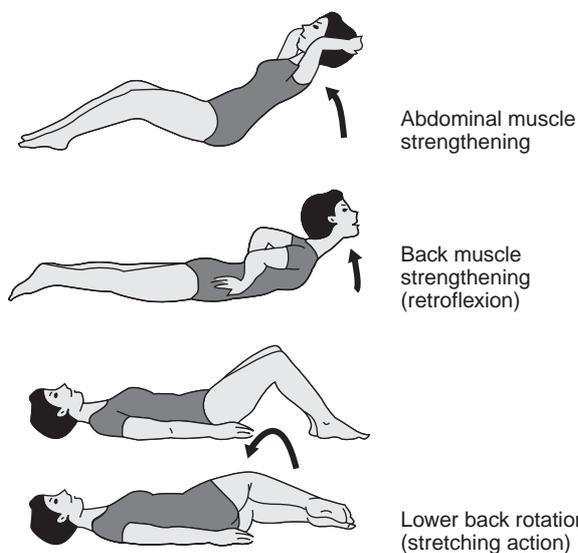


Fig. 4 Exercise therapy for chronic muscular low back pain (Hayashi, Y.: Stiff shoulder and low back pain. *The Journal of Therapy* 1991; 73(11): 2183)

tive. However, because its efficacy was unpredictable and temporary, the hospital stay was too long, etc., it is no longer performed for lumbar spinal canal stenosis, which is a degenerative disease, and blocking therapy or surgical therapy is performed instead. Traction seldom exacerbates symptoms, but because powerful force is exerted on the bones through the skin, it is necessary to check to be sure that no redness or foci of necrosis have developed in the skin. Moreover, when the weight is placed in a high position to prevent it from touching the floor, care must be taken to ensure that it does not fall and cause an accident.

Exercise Therapy (Muscle Strengthening)

Exercise therapy relieves low back pain in chronic muscular low back pain and degenerative diseases of the lumbar spine by strengthening the lumbar muscles and abdominal muscles. Lumbar muscles whose muscle strength has been increased by exercise are able to lifting the upper body, with the lower back acting as the pivot. The abdominal muscles act as a

“natural” corset, and as shown in Fig. 1, they contribute to raising the pressure in the abdominal cavity and reducing the load of the force on the lower back. Two simplified Williams’ exercises and stretch exercises performed before and after them appear to be useful for this purpose, and they are illustrated in Fig. 4.

Eliminating the movements of other muscles by slightly flexing the knees and slowly lifting the upper portion of the body by contracting the abdominal muscles alone is an effective means of strengthening the abdominal muscles. However, it is sometimes difficult to perform unless patients have regularly trained their abdominal muscles, and excessive repetitive abdominal strengthening exercises sometimes cause such intense pain the following day that the patient seems to have peritonitis. Because of this it is advisable to gradually strengthen the muscles by using techniques and numbers of repetitions tailored to each individual’s physical constitution. In regard to the lumbar muscles, there is a tendency to be kyphotic in osteoporosis and scoliosis is sometimes present in cases of intervertebral disc degeneration, making it difficult to bend the body back, and forcing the back into retroflexion may risk exacerbating the lower back pain.

Keeping these points in mind, lower back pain is often relieved by about 3–4 weeks after starting 20–30 repetitions of abdominal muscle and lower back muscle strengthening exercises a day. Before and after the training exercises it is useful to perform lower back rotation exercises in the same supine position by lowering the flexed knees to the right and left and stretching and moving the muscles and ligaments of the lower back and buttocks.

In the low back pain prevention exercise class in Tokyo that the author was involved in, practical training guidance centered on the exercises in Fig. 4 was provided for 10 weeks with the aim of establishing regular exercise habits at home. The result was improvement of the low back pain in 32 of the 50 participants (48 women, 2 men; mean age 53.8 years), and

measurements of several parameters in the patients who showed improvement revealed that the changes were significant.³⁾

Exercise therapy is the sole educational form of physical therapy for low back pain, and it demands an effort on the part of patients, but if patients can learn muscle strengthening and make it a regular habit, it is a “good medicine” that they can take with them wherever they go.

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Occult Hematuria Detected on Health Screening

JMAJ 47(5): 240–246, 2004

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Abstract: The detection rate of occult hematuria found on health screening is considerably high, ranging from 2.8% to 16%, which is double or triple that of proteinuria. Diseases in adults that cause hematuria can be broadly divided into three groups: systemic disease involving the kidney, renal parenchymal disease, and urologic disease. Systemic diseases causing damage to the kidney include hypertension, diabetes mellitus, and many other diseases. Important renal parenchymal diseases are glomerulonephritis and its related diseases. When systemic diseases and renal parenchymal diseases are excluded, there is a high possibility of urologic diseases such as malignant tumor, urolithiasis, and urinary tract infection. In children, it is also necessary to consider both pediatric and urologic diseases. In particular, hereditary nephritis and congenital urinary tract malformation are clinically important. Occult hematuria, which is frequently found on health screenings, has various possible causes. In approximately 80% of the cases detected, however, the cause was not discovered and a positive diagnosis was not possible. Therefore, it is important to develop effective strategies for diagnosing the cause of microscopic hematuria.

Key words: Occult hematuria; Mass screening

Introduction

Hematuria is defined by the presence of red blood cells (RBCs) in urine. RBCs in urine are generally regarded as pathologic when 3–5 or more per field are found by microscopic obser-

vation of urinary sediment under high (400-fold) magnification. Hematuria is classified as macroscopic (visible to the naked eye) or microscopic (recognized only under a microscope), or by the presence/absence of concomitant symptoms as symptomatic or asymptomatic.

This article is a revised English version of a paper originally published in the *Journal of the Japan Medical Association* (Vol. 128, No. 5, 2002, pages 767–771).

The Japanese text is a transcript of a lecture originally aired on February 18, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

Table 1 Diseases That Cause Microscopic Hematuria in Adults

(%)

Author(s)	No. of cases	Systemic disease	Glomerulonephritis	Urologic tumor	Urolithiasis	Urinary tract infection
Kinoshita <i>et al.</i> ²⁾	794	88 (11)	73 (9)	5 (0.6)	35 (4.4)	
Murakami <i>et al.</i> ⁴⁾	637			8 (1.3)	21 (3.3)	17 (2.7)
Morita <i>et al.</i> ⁵⁾	315	23 (7.3)	7 (2.2)	12 (3.8)	25 (7.9)	44 (14)
Saida <i>et al.</i> ⁶⁾	607		41 (6.8)	4 (0.6)	47 (7.7)	108 (18)
Hattori <i>et al.</i> ⁷⁾	339		7 (2.1)	2 (0.6)	16 (4.7)	23 (6.8)
Marumo <i>et al.</i> ⁸⁾	750		65 (8.7)	3 (0.4)	19 (2.5)	4 (0.5)

Occult hematuria found on mass screening is asymptomatic and microscopic in most cases, and accounts for 2.8–16% of subjects.^{1–3)} Systemic disease, renal parenchymal disease, and urologic disease are the main causes of this condition. In spite of close examination, the etiology remains unclear in about 80% of cases, indicating the difficulty in determining the cause of occult hematuria.

This paper reviews diseases that may cause clinically relevant occult hematuria detected on mass screening and discusses how to examine and treat it in adults. Occult hematuria in children is also outlined briefly.

Occult Hematuria in Mass Screening

Hematuria is found frequently among mass screening subjects, with the reported incidence ranging from 2.8% to 16%. Although the frequency varies according to the target of screening, the detection rate is usually double or triple that of proteinuria.^{1–3)} The percentage of subjects positive for occult hematuria generally increases with age.¹⁾ The rate is higher in women, and that may be explained by the higher incidence of urinary tract infection and contamination by menstrual blood.

The diseases causing microscopic hematuria and their frequencies as reported in the literatures are listed in Table 1.^{2,4–8)} Among the various causes of microscopic hematuria, systemic diseases such as diabetes mellitus and hyper-

tension, which cause damage to the kidney, account for 7.3–11%. Glomerulonephritis, a clinically significant disease related to abnormal urine test results, is found in 2.1–9% of subjects. Urologic tumor is found in 0.4–3.8% of subjects. Although its frequency is relatively low, this disease is life-threatening and therefore clinically significant. When the subject is 40 years old or older, the presence of hematuria, even if it is microscopic, warrants consultation with a urologist. Urolithiasis is diagnosed in 2.5–7.9% of subjects, and urinary tract infection in 0.5–18% of subjects. Both conditions are relatively common and should be kept in mind when occult hematuria has been found on health screening.

Guidelines have not been established for the follow-up observation of patients with asymptomatic hematuria. It is, however, important that any condition likely to lead to renal failure should not be overlooked. Based on their long-term observation of subjects with abnormal urine test results, Yamagata *et al.* reported that about 50% of subjects positive for hematuria alone experienced disappearance of hematuria, about 40% showed no change, and about 10% eventually developed proteinuria and were diagnosed as having chronic nephritis. In addition, they reported that 75% of subjects who were positive for proteinuria with or without hematuria were later diagnosed as having chronic nephritis.³⁾ Subjects positive for hematuria alone showed very little worsening of

renal function, whereas 10% of subjects positive for proteinuria and 30% of those positive for both hematuria and proteinuria developed increased creatinine levels within 10 years.³⁾

Thus, when hematuria alone is positive, the probability is low that it will develop into a serious disease in the future. Therefore, we consider it sufficient to follow the course of the condition through non-invasive tests, such as urinalysis, blood examination, and ultrasonography.

Diagnostic Procedures for Hematuria

Urinalysis performed as part of a health screening usually employs a paper strip test. Therefore, when the test has indicated hematuria, it is necessary to carry out microscopic observation of urinary sediments to determine the severity of hematuria. It is also important to look for irregularities in the size and shape of RBCs, and the presence of white blood cells and casts in urine. In addition, the following examinations should be performed: a general physical examination; blood pressure measurement; complete blood count; blood biochemical tests for BUN, creatinine, and serum electrolytes; serological assays of ASLO, immunoglobulins, and complement; urinary cytology, and ultrasonography of the kidney and urinary tract.

In general, the possibility of renal parenchymal disease is high when the following are noted: proteinuria, urinary casts, edema in the lower limbs and face, hypertension, renal dysfunction, elevated levels of ASLO and IgA, decreased complement, and bilateral renal atrophy. Subjects who have clinical signs and laboratory findings suggesting the presence of renal parenchymal disease should be referred for detailed examination by a nephrologist. The final diagnosis should be made by renal biopsy.

When such abnormalities are not found, when urinary cytology shows positive results, or when ultrasonography suggests urologic disease, urologic examinations such as drip infu-

Table 2 Systemic Diseases That May Cause Hematuria

Hypertension	Necrotizing angitis	Diabetes mellitus
Hyperuricemia	Amyloidosis	Sarcoidosis
Collagen disease	Multiple myeloma	Leukemia
Goodpasture's syndrome	Hemophilia	Thrombocytopenic purpura

sion pyelography (DIP), cystoscopy, CT, and MRI should be performed.

Diseases That May Cause Hematuria

Diseases that may cause hematuria are broadly divided into three groups: systemic disease, renal parenchymal disease, and urologic disease.

1. Systemic disease

Systemic diseases that may cause hematuria and proteinuria and lead to renal failure include hypertension, necrotizing angitis, diabetes mellitus, hyperuricemia, amyloidosis, sarcoidosis, collagen diseases such as systemic lupus erythematosus (SLE), multiple myeloma, leukemia, Goodpasture's syndrome etc. (Table 2).^{1,9)} Diseases showing hemorrhagic diathesis, such as hemophilia and thrombocytopenic purpura, while not causing renal disorders, can be the cause of hematuria.⁹⁾ In general, these diseases are seldom detected by occult hematuria on health screening, but they are often found as a result of other signs and symptoms or laboratory findings. Nevertheless, it should be noted that while many diseases can cause microscopic hematuria, it is difficult to diagnose any of them positively as the cause. They should be regarded as probable diagnoses after other possible causative diseases have been excluded.

2. Renal parenchymal disease

Glomerulonephritis, a well-known renal parenchymal disease, must be differentiated from a similar condition called persistent hematuria/proteinuria syndrome, which is associ-

Table 3 Renal Diseases That Cause Hematuria

1. Primary glomerulonephritis
Chronic glomerulonephritis (including IgA nephropathy)
Persistent hematuria/proteinuria syndrome
2. Hereditary nephritis
Alport's syndrome
Thin basement membrane disease

ated with persistent hematuria and proteinuria without renal dysfunction. From the viewpoint of treatment, it is critical that these two conditions be differentiated (Table 3).⁹⁾ Glomerulonephritis is highly likely when RBCs in urine are irregular in size or shape, when hematuria is accompanied with proteinuria or urinary casts, when there is hypertension or accompanying edema in the lower limbs, when blood test reveals renal dysfunction, or when there is elevated ASLO or IgA or decreased complement. It is also necessary to consider hereditary nephritis such as Alport's syndrome, in which nephritis is accompanied with impaired hearing, and thin basement membrane disease, in which benign recurrent hematuria is present. These diseases are more likely to show the presence of a family history (Table 3). The definitive diagnoses of these conditions are established by histopathological determination of the glomerular abnormalities, and treatment modalities are then determined. Therefore, when these diseases are suspected, it is necessary to refer the subject to a nephrologist.

3. Urologic disease

Urologic diseases are highly likely to be involved when the above-mentioned systemic diseases and renal parenchymal diseases are excluded, necessitating close examination by urologists.

The most important urologic diseases detected by hematuria are malignant tumors such as renal cell carcinoma, renal pelvic and ureter cancer, bladder cancer, and prostate cancer. Among these tumors, renal cell carcinoma,

renal pelvic and ureteral cancer, and bladder cancer often manifest with macroscopic hematuria as the initial sign. Although it is uncommon to find these diseases through close examination of microscopic hematuria, it is important not to overlook them because they are life threatening.

If the urinary cytology and DIP, which are useful tests for renal pelvic and ureteral cancer, indicate the possibility of cancer, further examination by CT, retrograde pyelography, or ureteroscopy should be performed to establish the diagnosis. Bladder cancer is the most frequent disease in the field of urology. Both the urinary cytology and cystoscopy are useful for diagnosing this disease. Almost all cases of bladder cancer can be diagnosed by cystoscopy. Renal cell carcinoma is usually detectable by ultrasonography when the tumor measures 3 cm or more in diameter. Definitive diagnosis is obtained by CT or MRI. Hematuria rarely serves as a clue to the presence of prostate cancer, whose major symptoms are dysuria, pollakisuria, sense of residual urine etc. This disease, however, should also be considered as the cause of hematuria.

Another important disease entity is urolithiasis, which are classified into renal stones, ureteral stones, and bladder stones, according to their site. Although renal and ureteral stones are commonly accompanied with severe back pain or flank pain, it is not uncommon for these conditions to be detected by examination on occult hematuria. Urolithiasis occur more frequently than malignant tumors and more often cause microscopic hematuria, thus requiring attention. Ultrasonography, DIP, or CT is required to establish the diagnosis.

Urinary tract infection is also a frequent cause of hematuria. Since white blood cells and bacteria are found in the urine, it is not difficult to make this diagnosis. Appropriate antibiotic therapy based on the results of bacterial culture of the urine should be given to the patient. In general, pyelonephritis is accompanied with fever and back pain, and cystitis is accompa-

Table 4 Urologic Diseases That Cause Hematuria

1. Malignant tumor	Renal cell carcinoma, Renal pelvic and ureteral cancer, Bladder cancer, Prostate cancer
2. Urolithiasis	Kidney stones, Ureteral stones, Bladder stones
3. Urinary tract infection	Pyelonephritis, Cystitis, Renal and urinary tract tuberculosis
4. Others	

nied with micturition pain, pollakisuria, and cloudy urine. However, when there are few symptoms, chronic urinary tract infection should be suspected. In such cases, urolithiasis, hydronephrosis, vesicoureteral reflux, prostate hypertrophy, or neurogenic bladder may be an underlying condition, and close examination of the urinary tract is required. If asymptomatic microscopic hematuria and pyuria are persistent, renal and urinary tract tuberculosis is a possibility that should not be overlooked (Table 4).

In addition to the above diseases, a variety of diseases of the kidney and urinary tract can cause hematuria. These include renal cyst, polycystic kidney, horseshoe kidney, atrophic kidney, idiopathic renal bleeding, hydronephrosis, double renal pelvis and ureter, ureteral stenosis, vesicoureteral reflux, vesical diverticulum, interstitial cystitis, radiation cystitis, bladder neck contracture, prostatic hypertrophy, prostatitis, prostatic stones, urethral stricture, and urethral caruncle etc. It is therefore important to refer to urologists for closer examination.^{10,11)}

Occult Hematuria in Children

When examining children, it is necessary to consider both urologic and pediatric diseases. For health screening of school children in Japan, the Tokyo system has been widely adopted, by which children with abnormal results on a primary urine test are subjected to a

secondary urine test, and those with abnormal results on the secondary test are subjected to a tertiary examination consisting of urinalysis including urinary sediment, medical examination by a physician, measurement of blood pressure, and blood test. The follow-up plan and the management of daily activities are clarified to a greater extent than in adults.^{1,3)}

The positivity rate for occult hematuria on primary urinary screening was reported to be 1.9% among 4,930,000 elementary school children and 5.1% among 2,420,000 junior high school students. The corresponding rates on secondary screening are 0.5% among 120,000 elementary school children and 0.9% among 170,000 junior high school students. These percentages are two- to threefold higher than those for proteinuria.¹²⁾ As a result of tertiary screening of those positive for occult hematuria together with those positive for proteinuria, nephritis was found in 1.0% and urinary tract infection in 2% of 12,140 elementary school children, while nephritis was found in 0.8% and urinary tract infection in 1.8% of 10,145 junior high school students.¹²⁾

Although few detailed reports exist on the causes of microscopic hematuria in children, urinary tract infection, hydronephrosis, vesicoureteral reflux, urinary tract stones, and nephritis have been detected as causes (Table 5).^{1,13)}

Among children with abnormal urine test results, including proteinuria on health screening in schools, the frequency of glomerulonephritis is high, and hereditary nephritis such as Alport's syndrome and thin basement membrane disease are also important causative conditions. Among renal disorders associated with systemic diseases, nephritis due to purpura, nephritis due to SLE, and Goodpasture's syndrome are important. Hemorrhagic diseases such as hemophilia and thrombocytopenic purpura can also cause hematuria. Urinary tract infection and urolithiasis may also be detected through occult hematuria.

In addition, children may present congenital renal and urinary tract diseases including poly-

Table 5 Diseases That Cause Microscopic Hematuria in Children

Author(s)	Urinary tract infection	Hydronephrosis	Vesicoureteral reflux	Urolithiasis	Nephritis	Polycystic kidney	Others	Total
Murakami <i>et al.</i> ¹⁾	0 (0)	3 (1.1)	0 (0)	1 (0.4)	6 (2.2)	1 (0.4)	264	275
Kawamura <i>et al.</i> ¹³⁾	13 (12)	8 (7.5)	4 (3.8)	3 (2.8)	2 (1.9)	0 (0)	76	106

cystic kidney, congenital hydronephrosis, and vesicoureteral reflux. Congenital hydronephrosis and vesicoureteral reflux can be detected by abnormal urine test results including hematuria, although pyelonephritis is a more common clue to find them. Therefore, it is necessary to perform diagnostic imaging procedures such as ultrasonography, intravenous pyelography, and cystography in cooperation with pediatricians and urologists (Table 6).^{1,14)} No imaging techniques are employed by the Tokyo system even for tertiary screening; this should be reconsidered in the future.¹⁾

However, if hematuria is the only abnormality found in health screening in school, the probability of detecting serious diseases that require treatment or close follow-up is as low as 5%,¹⁾ suggesting that the clinical significance of microscopic hematuria is low in children as well as in adults. Thus, follow-up observation generally seems to be sufficient for positive examinees, with no need for renal biopsy or strict control of daily activities including limitations on diet and exercise.

Conclusion

Occult hematuria found on health screening has been outlined, with most attention focused on adult cases. Although the detection of hematuria on health screenings is frequent, it rarely leads to diagnosis of the causative disease. It is important to establish effective measures for diagnosing the cause of occult hematuria and to provide useful methods of follow-up observation.

Table 6 Pediatric Diseases That Cause Hematuria

- | |
|-------------------------------------------------------------------------------------------------|
| 1. Primary glomerulonephritis |
| 2. Hereditary nephritis
Alport's syndrome,
Thin basement membrane diseases |
| 3. Systemic disease |
| 4. Urinary tract infection
Pyelonephritis, Cystitis |
| 5. Congenital anomaly
Polycystic kidney, Congenital hydronephrosis,
Vesicoureteral reflux |

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Interferon Therapy for Chronic Hepatitis B

JMAJ 47(5): 247–252, 2004

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Abstract: Interferon has been used to treat chronic hepatitis B in Japan for more than 10 years, but the duration of treatment has been limited to only 1 month by the health insurance system in Japan. The efficacy of daily 28-day therapy is unsatisfactory, with seroconversion occurring in less than 30% of hepatitis B e antigen-positive patients. The insurance system has recently begun to cover interferon therapy for 6 months, and the longer treatment is expected to increase the seroconversion rate above 30% and to decrease viral proliferation more effectively. Interferon therapy, instead of other treatment modalities, such as lamivudine, is mostly indicated for chronic hepatitis B in naïve young patients. Newer anti-viral agents are expected to increase the diversity and efficacy of treatment.

Key words: Hepatitis B virus; Anti-viral therapy; Gene mutation; Lamivudine

Introduction

The pathophysiology of chronic hepatitis B reflects the balance between proliferation of the hepatitis B virus (HBV) and the host's immunological response against the virus. Most cases of hepatitis B in Japan and Southeast Asian countries are diagnosed in HBV carriers beginning in infancy. During childhood, immune tolerance keeps these carriers symptom-free (no hepatic inflammation). However, after puberty, when the immune system becomes mature, immune clearance of HBV begins in these HBV carriers, with liver cell destruction and the onset of chronic hepatitis. When the immunological response is stronger than the proliferative potential of the HBV, virus prolif-

eration is controlled, leading to seroconversion of HBeAg (hepatitis B e antigen) and remission of hepatitis. The natural history of HBV is thought to typically follow such a course.

HBV attempts to escape from the host's immune attack by inducing mutations within itself (in the pre-core and core promoter regions, etc.). When this occurs, there may be renewed interplay between the variant HBV and the immune system, possibly resulting in modification of the above-mentioned natural history of HBV in individual cases. During the natural history of HBV infection in chronic HBV carriers, the transaminase levels sometimes show a flare. When viewed histologically, fibrosis advances episodically during such a flare, depending on the magnitude of the flare

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 7, 2002, pages 1049–1053).

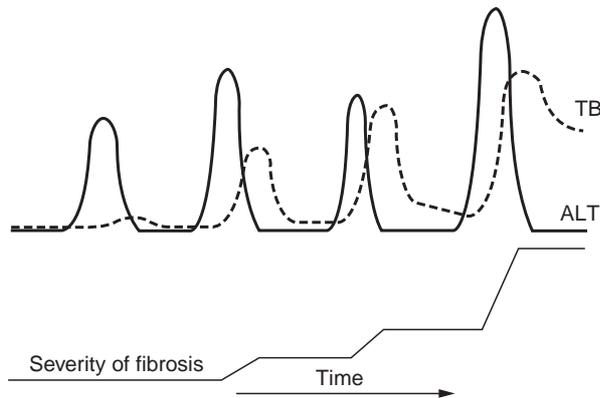


Fig. 1

In cases of chronic hepatitis B, a flare in the transaminase levels is associated with histological deterioration of the liver, and episodic exacerbation of fibrosis. The ALT levels normalize as the flare subsides, but the reserve function of the liver, represented by the total bilirubin (TB) level, diminishes after the flare. Thus, hepatitis progresses episodically towards cirrhosis following cycles of appearance and remission of the flares.

(Fig. 1). As a result, we sometimes encounter cases in which hepatitis has advanced to liver cirrhosis without being detected, even though the duration of inflammation have not been expected to be long. This situation is in contrast to that in cases of chronic hepatitis C (which in recent years, has been found to account for a high percentage of the total cases of chronic hepatitis), in which no such flares are known to occur, the inflammation is persistent, and fibrosis advances gradually (rather than in episodes) over decades. It has also been reported that if the HBV DNA level in cases with HBV infection remains below the detectable limit for prolonged periods of time, the risk of development of liver cancer decreases. When virus proliferation is kept suppressed, the transaminase levels remain low, and the inflammation and fibrosis in the liver do not progress, resulting in a decrease in the risk of development of liver cancer.

On the basis of these findings, it is considered that some possible means of improving the prognosis of chronic hepatitis B include suppression of the frequency of the enzyme flares and peak levels, minimization of the inflamma-

tion (if minimization of flares is not possible), and minimization of the proliferation of HBV. Therefore, antiviral therapy for chronic hepatitis B is aimed at keeping HBV absent from the blood and alleviating hepatitis. In other words, the treatment should be aimed at normalizing the transaminase levels, reducing the serum HBV DNA level to below the detectable level (always less than 10^5 copies/ml in Western countries), achieving disappearance of the HBeAg from the blood, and alleviating the hepatocellular inflammation. The only antiviral drugs currently covered by the Health Insurance system in Japan for the treatment of chronic hepatitis B are interferon (IFN)- α , IFN- β , and lamivudine.

IFN Therapy for Chronic Hepatitis B

Although IFN has been shown to suppress the proliferation of hepatitis viruses and reduce the severity of hepatic inflammation, the response of cases of chronic hepatitis B to IFN therapy has been poor. The effect of IFN against hepatitis B is only transient, and treatment with the drug given according to currently employed regimens yields rather unsatisfactory results. In Japan, IFN therapy for chronic hepatitis B is covered by the Health Insurance if it is administered to HBeAg positive cases of chronic active hepatitis for 28 consecutive days (one month) at the maximum.

Chronic hepatitis B in Japan mostly develops in HBV carriers who have contracted the infection by vertical mother-child transmission. In such cases with prolonged HBV infection, it is difficult to successfully eradicate the virus by IFN therapy or any other currently available antiviral therapy. That is, the percentage of cases in which the HBsAg (hepatitis B surface antigen) disappears from the serum, with the appearance of anti HBsAg antibody, during the natural course of HBV infection or following antiviral therapy is only up to about 5% in this country. Cases of chronic active hepatitis with elevated serum transaminase levels should be

considered as candidates for treatment, even when the HBeAg cannot be detected in the serum.

1. IFN therapy in Japan

In Japan, IFN has been administered to HBeAg positive cases of chronic active hepatitis for a maximum period of one month due to the restrictions imposed by the Health Insurance system. IFN therapy thus has not yielded satisfactory results, and the number of cases receiving IFN therapy for chronic hepatitis B has been on the decline.

The efficacy of IFN therapy has been reported to increase with increasing duration of administration of the drug. At our facility, the percentage of patients found to be HBeAg negative at the end of one year after IFN- α (9 MIU) therapy for a month was 28.6% ($n=28$). Kanai *et al.* reported that among cases in which IFN- α (9 MIU) was administered for 14 consecutive days followed by thrice weekly dosing for 22 weeks (6 months in total), 52% became HBeAg negative by 6 months after the end of therapy. They further reported that the percentage of cases becoming HBeAg negative rose further when IFN was administered for 26 additional weeks.¹⁾ Iino *et al.* compared the efficacy of IFN therapy administered for 4, 12, and 24 weeks, and reported that the percentage of patients who became seronegative for HBV DNA was the highest (21%) in the 24-week dosing group.²⁾ At our facility also, the percentage of patients who became HBeAg negative was significantly lower in the 28-day consecutive dosing group than in the 28-week, once weekly dosing group, for the same cumulative dose.

Currently, there is no restriction on the period of IFN therapy for cases of chronic hepatitis C under the Health Insurance system in Japan. For cases of chronic hepatitis B, administration of IFN for a maximum period of 6 months is also now deemed to be possible under the Health Insurance system (this interpretation began to be adopted 2 years ago).

The results of 6-month IFN therapy for chronic hepatitis B can therefore be expected to be published in the near future in Japan.

2. IFN therapy in foreign countries

A meta-analysis was carried out of the results of several published studies on IFN therapy administered for 3–6 months to HBeAg positive cases of chronic hepatitis B. This analysis revealed that the percentage of patients showing disappearance of HBeAg following IFN therapy was as high as 30–40%, as compared to only 5–6% among untreated patients. This result leads one to conclude that IFN may be effective in HBeAg positive cases of chronic hepatitis B.

The meta-analysis conducted by Wong *et al.*³⁾ involved 15 randomized controlled trials. Of the 837 patients included in these 15 trials, 498 received IFN- α (5–10 MIU) thrice weekly for 4–6 months, and 339 received no IFN- α therapy (control group). Wong *et al.* reported that following IFN therapy, the percentage of cases showing disappearance of HBV DNA was 37% in the treated group as compared to 17% in the control group, the HBeAg disappearance rate was 33% in the treated group as compared to 12% in the control group, and the HBsAg disappearance rate was 8% in the treated group as compared to 1% in the control group. Krogsgaard *et al.*⁴⁾ recommended that IFN be administered at a cumulative dose level of over 100 mega-IU.

3. Indications for treatment and prediction of efficacy

A near-consensus has been reached among the Asian Pacific Association for the Study of Liver (APASL), the European Association for the Study of the Liver (EASL) and Japanese hepatologists about the suitable candidates for IFN therapy among patients with chronic hepatitis B. It is clearly agreed that IFN therapy is not indicated in patients with normal transaminase levels. Patients who are seropositive for HBV DNA and whose transaminase levels are

twice as high or more than the upper limit of the normal range are considered to be suitable candidates for IFN therapy, while lamivudine rather than IFN is recommended for patients whose transaminase levels are closer to five times the upper limit of the normal range. IFN therapy has also been recommended in young patients with chronic active hepatitis.

Regarding the prediction of efficacy of IFN therapy, it has been reported that female patients are likely to respond better to IFN therapy than male patients, and that cases with higher histological activity levels more frequently become HBeAg negative following IFN therapy. Regarding the relationship between the efficacy of IFN and the pre-treatment levels of the transaminases, virus load, etc., it has been reported that the HBe antigen disappearance rate increase as the HBV DNA load decrease and the serum ALT levels rise.

4. Responses of HBeAg negative cases to IFN therapy

Some cases of chronic hepatitis B have active hepatitis while being HBeAg negative. The absence of HBeAg in these cases is thought to be attributable to mutation of the HBV (mutation of the pre-core and core promoter regions of the HBV gene).

In regard to the effectiveness of IFN therapy in these patients, the author found that 38 to 90% of the cases became seronegative for HBV DNA immediately after IFN therapy for 6–12 months, as compared to 0–37% in the untreated group. The percentage of patients who were seronegative for HBV DNA at the end of one year after treatment was 10–47% in the IFN therapy group (0% in the untreated group). These results indicate that the suppressive effect on the proliferation of HBV often persists even after the end of IFN therapy.⁵⁾

Thus, IFN therapy may be a valid strategy for treating cases of chronic hepatitis B, irrespective of the serum HBeAg status. However, the indications for this therapy need to be determined based on a thorough evaluation of such

factors as the serum ALT levels, HBV DNA levels, and the histological features.

5. HBV gene mutation and response to IFN therapy

In general, the genomes of viruses often undergo mutation since they lack a sophisticated mechanism to verify replication. However, analysis of these mutations often gives the impression that these mutations do not occur at random. It seems likely that viruses undergo mutations of their own genes (including mutations of amino acids) to escape the stress of immune attacks of the host. HBV is one of such viruses to frequently exercise this ability to undergo mutations. Mutations of HBV, seemingly aimed at escaping from the effects of IFN therapy have also been noted. Such a mutant virus is called “escape mutant.” Antigens present on the surface (S) of viruses include three proteins: large S, middle S, and small S proteins. The gene region encoding large S is called Pre S. If this Pre S region is partially defective, an HBV escape mutant is sometimes formed. Cases in which gene mutations have taken place in other regions (including the core region) after IFN therapy have been reported.⁶⁾ These variants of HBV are considered to serve as escape mutants against IFN therapy.

The most frequently analyzed type of mutations in the HBV genome involve the pre-core and core promoter regions. Mutations of these regions yield HBV variants that lack the potential to produce HBeAg. These mutants are responsible for cases of active hepatitis B who remain HBeAg negative. Several reports have been published concerning the relationship between mutations in the pre-core region and the effectiveness of IFN therapy. While some investigators have reported that these mutants are more sensitive to IFN, others have reported that they are resistant to IFN therapy. According to Japanese reports, the sensitivity of these mutants to interferon therapy was enhanced as the number of mutations increased. Before arriving at any definitive conclusion regarding

this relationship, it would be important to analyze the relationship between the effectiveness of IFN therapy and such parameters as the route of infection, length of interval from the time of infection to the start of treatment, genotype, virus level, and dosing method of IFN.

Mutations in the core promoter region may also influence the effectiveness of IFN therapy. Mutations in this region seem to be associated with the duration of inflammations and resistance to IFN.⁷⁾ Recently, Kao *et al.*⁸⁾ reported that HBV genotype C underwent more frequent mutations of the core promoter region than HBV genotype B, and that the former was also more resistant to IFN therapy. Their findings suggest a correlation between the genotype of HBV and the response to IFN therapy. Some investigators, however, have reported that the genotype of HBV has no clinical significance.⁹⁾

6. Adverse reactions to IFN

When compared to the adverse reactions to IFN reported among patients with other diseases, no noteworthy adverse reactions to IFN specific to patients with chronic hepatitis B have been reported. As stated above, in Japan many cases of chronic hepatitis B receive this drug for 28 consecutive days in accordance with the dosing regimen covered by the Health Insurance system. However, when IFN- β is administered thus, the incidence of proteinuria is considerably high. On the other hand, in consecutive treatment with IFN- α , almost no cases of proteinuria have been reported. However, both IFN- α and IFN- β are associated with problems such as reduced WBC and platelet count, when administered at high dose levels or in elderly patients. Unlike with IFN therapy administered for treatment of chronic hepatitis C, late adverse reactions such as depression, alopecia, and thyroid dysfunction are seldom associated with IFN therapy for chronic hepatitis B, unless the drug is used for prolonged periods.

Conclusion

Only results of limited value have been obtained with IFN therapy for chronic hepatitis B. Although dynamic correlations have been shown between the effectiveness of IFN therapy and HBV gene mutations, such as in the case of escape mutants, no definite conclusions have been arrived at yet concerning the correlation between the efficacy of IFN therapy and any particular mutation of the HBV gene.

In Japan, long-term IFN therapy has recently begun to be used. It would be interesting to monitor the methods of dosing that might be developed to enhance the therapeutic efficacy of IFN. If peg-IFN were clinically introduced, and if more prolonged use (more than 6 months) of this drug were to be covered by the Health Insurance, the antiviral efficacy of IFN therapy against HBV may be further enhanced.

Lamivudine, a nucleoside analog serving as a reverse transcriptase inhibitor, has recently been introduced as a drug targeted against HIV and has been listed as a drug covered by the Health Insurance. Most cases treated with lamivudine showed normalization of the transaminase levels, disappearance of the HBV DNA from blood, and a high HBeAg seroconversion rate. Furthermore, this drug can be administered orally, which would allow a high compliance rate of the patients with this therapy. Lamivudine with these features has made a significant impact as a new antiviral drug against HBV.

This drug, however, cannot eradicate the complete-length HBV DNA invading the nuclei of the hosts' liver cells. For this reason, HBV may resume proliferative activity when lamivudine is discontinued. Strains of HBV resistant to this drug have also appeared following prolonged use of the drug. It would be desirable for a new drug to be developed with this problem resolved. Since IFN also exerts antiviral activity against lamivudine-resistant strains of HBV (YMDD mutants), study of prolonged IFN therapy to deal with lamivudine-resistant

HBV has been proposed.

In the near future, the new antiviral agents entecavir and adefovir are expected to become commercially available. When this occurs, treatment of chronic hepatitis B with IFN will decrease markedly. However, long-term IFN therapy is still considered to be useful in many situations, e.g., in dealing with lamivudine-resistant HBV, and in combined therapy with other antiviral agents. Since adequate immune potential of the host is considered to be indispensable for complete eradication of HBV, IFN with immunomodulating activity in addition to antiviral activity may provide a valid means of complete eradication of the virus if used optimally. In this respect, clinical introduction of peg-IFN, suitable for long-term use, would be desirable.

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