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## New Surgical Robotics for Clinical Use in Neurosurgery

Makoto Hashizume\*<sup>1</sup>

Minimally invasive surgery (MIS) has become so explosively popularized throughout the world because there is a significant difference in the postoperative quality of life of the patients with MIS from that with open surgery. The patients can enjoy earlier recovery to normal life or normal activity after MIS than after conventional open surgery. Although there are clear benefits, MIS has also some disadvantages for the surgeons. Long instruments placed through fixed entry points creating a fulcrum effect, with the surgical field viewed on a 2-D screen and with the camera under an assistant's control, create an unnatural environment where the surgeon loses orientation, the eye-hand-target axis, and visual depth perception. All these obstacles reduce the surgeon's normal dexterity and limit his ability to deal with difficult situations.

Computer-aided surgery, known as Robotic surgery, is proposed to overcome some of the drawbacks of traditional MIS.<sup>1</sup> This technology includes master-slave telemanipulator systems. The goals of these surgical systems are to enhance manipulation capabilities and to increase the performance precision. It provides secure precise procedures without any limitation in whichever direction the operator desires. The da Vinci is the most popular surgical robotic system among the commercially available types. More than 430 sets of the da Vinci are already installed all over the world at present. More than 300 sets are installed in the United States and more than 50 sets are in Europe. Robotic surgery provides you with a 3 dimensional view as well as 7 degrees of freedom of the instruments with an articulate at the tip. It is easier for you to perform complicated procedures such as ligature or suturing with a needle in a confined space. That is the reason why more than 40 percent of all prostatectomies have been performed with the surgical robotic system in the United States.

However, the size of the robotics is so large at this moment that it has been impossible to apply

the system to microsurgery such as neurosurgery where there are so many critical conditions to be resolved. The target area is surrounded by the so important normal tissue that the access to the deeper targeting area is limited. The paper by Nishizawa et al. in this issue of the journal is considered significant, as they have developed new surgical robotics with the concept of MIS via a single insertion part and the prior-confirmation based safety control. It required several technical developments to enable the performance of MIS via a single hole. They made neurosurgery in one-opening craniotomy under fine and accurate control to avoid damage to the surrounding important normal tissues.

The issue of interference between mechanical elements was solved by developing a hollow flexible torque tube with one end segment of the hollow pipe. This mechanism allows the torque and thrust for rotation and translation movements successfully transmitted to the joint at the tip of the manipulator, resulting in the production of fine and high performance with an accuracy of less than 10 $\mu$ m. There is no need for concern over collision among the arms holding the manipulators and medical staff. There is a serious problem in Japan that some parties have discontinued the development of therapeutic tools. This paper is thus highly evaluated as the authors have confirmed the basic function of the new robotics in clinical settings.

The authors evaluated the feasibility of robotics for clinical use, especially focused on safety control. Actual movement of the manipulator takes places only after prior calculation of the position that would result from the input manipulate. They

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\*1 Department of Disaster and Emergency Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka  
Correspondence to: Makoto Hashizume MD, PhD, FACS, Department of Disaster and Emergency Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka-shi, Fukuoka 812-8582, Japan. Tel: 81-92-642-6222, Fax: 81-92-642-6224, E-mail: mhashi@dem.med.kyushu-u.ac.jp

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call the safety control system “prior-confirmation based safety control.” It prevents any movement of the manipulator beyond the predetermined range in the field of neurosurgery. These fine and accurate control systems as well as safety control make it possible to perform MIS via one-opening craniotomy in neurosurgery, which was impossible in conventional methods. This provides the possibility of expanding MIS to other fields of microsurgery. Although the working area is limited to that within 1 cm<sup>3</sup> in the present robotic system, the utility and possibility would be further expanded with the development of technology on molecular image or genetic information.

The goal of future surgery will be to change

the function rather than the structure of the organ or disease.<sup>2</sup> In this concept, termed biosurgery by Randall Wolf, MD, the purpose will be to change the biological processes of the body through direct modification of cellular, molecular, metabolic, and perhaps even genetic processes. The new robotic system developed by Nishizawa et al. will lead us to the second step towards attaining the goal.

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# Development of Surgical Manipulator System “HUMAN” for Clinical Neurosurgery

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Koji Nishizawa,<sup>\*1,2</sup> Masakatsu G Fujie,<sup>\*3</sup> Kazuhiro Hongo,<sup>\*4</sup> Takeyoshi Dohi,<sup>\*5</sup> Hiroshi Iseki<sup>\*6</sup>

## Abstract

Surgery using manipulator systems for medical treatment has recently attracted considerable attention as a method for realizing certain minimally invasive surgeries. In the field of navel surgery, some manipulator systems for medical treatments are used in Europe and the United States. However, it is inappropriate to apply these systems to neurosurgery because the size of the manipulators is too large, and only one of them can be used in one insertion part. To solve this problem, we developed the manipulator system “HUMAN”, which has an insertion part with a diameter of 10 mm and contains one endoscope and three manipulators. In this paper, we propose the concept for realizing minimally invasive surgery, and discuss the mechanism and control of our developed system based on this concept. A clinical application using this system was successfully performed in August 2002, and was successful. Since the manipulator is so small that operation is possible from one small incision, this system is effective in realizing certain minimally invasive neurosurgeries.

**Key words** Surgical support, Master-slave manipulator system, Neurosurgery, Clinical application

## Introduction

The development of minimally invasive surgery, involving as little damage to the body as possible, is strongly desired as a means to alleviate the physical and psychological suffering of patients and to accelerate postoperative recovery. In a form of such surgery known as laparoscopic surgery, a surgical operation is performed using a laparoscope, and surgical tools such as slender forceps are inserted through small incisions. This type of surgery has been popularized rapidly since the first successful laparoscopic cholecystectomy was performed by Muhe et al. in 1985.<sup>1</sup>

Although laparoscopic surgery has the advantage of low invasiveness, the high degree of

difficulty in the manipulation of surgical tools is a major drawback of this procedure as compared with open surgery. As an alternative way to safely perform minimally invasive surgery, much attention has recently been directed at the use of surgical manipulators incorporating robot technology. There are several surgical manipulators currently applied to clinical use mainly in Western countries, such as the da Vinci<sup>®</sup> and ZEUS<sup>®</sup> systems, which have been fairly well appraised by clinicians for good maneuverability.<sup>2-5</sup>

Realization of minimally invasive surgery has also been pursued in the field of neurosurgery. For example, procedures such as thermal treatment and biopsy using neuro-endoscopes have entered practical use.<sup>6</sup> However, the applicability of this method is limited to simple movements,

<sup>\*1</sup> Graduate School of Medicine, Tokyo Women's Medical University, Tokyo; <sup>\*2</sup> Mechanical Engineering Research Laboratory, Hitachi, Ltd., Hitachinaka; <sup>\*3</sup> School of Science and Engineering, Waseda University, Tokyo; <sup>\*4</sup> Department of Neurosurgery, Shinshu University School of Medicine, Matsumoto; <sup>\*5</sup> Institute of Environmental Studies, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo; <sup>\*6</sup> Institute of Advanced Biomedical Engineering & Science, Tokyo Women's Medical University, Tokyo

Correspondence to: Hiroshi Iseki MD, Koji Nishizawa, Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering & Science, Graduate School of Medicine, Tokyo Women's Medical University, 8-1 Kawada-cho Shinjuku-ku, Tokyo 162-8666, Japan.  
Tel: 81-3-5312-1844, Fax: 81-3-5312-1844, E-mail: hiseki@abmes.twmu.ac.jp, knishizawa@abmes.twmu.ac.jp

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and the reality is that enucleation of tumors and other operations involving delicate and complicated manipulation are normally performed by means of extensive craniotomy and microsurgery under a surgical microscope.<sup>2</sup> The realization of minimally invasive surgery remains a problem to be solved.

As compared with abdominal operations in general, neurosurgery requires considerations regarding the following characteristics: 1) important normal tissues are located densely around the lesion; 2) tissues are prone to damage and susceptible to pressure; 3) the field of operation is limited to a small area; 4) there are strict limitations on the site of the craniotomy providing an approach to the lesion site; and 5) manipulation must be controlled finely and accurately to avoid damage to normal tissues.

To realize minimally invasive surgery that can provide an alternative to conventional craniotomy, we must be able to perform a dexterous surgical operation in which the surgeon can manipulate multiple slender surgical tools inserted through one small cranial opening in such a way that the lesion may be treated accurately without causing pressure or damage to the surrounding normal tissues. Such an extremely delicate surgical operation can not be performed by human hands.

Existing surgical manipulator systems such as da Vinci<sup>®</sup> and ZEUS<sup>®</sup> are not suitable for use in neurosurgery, because of the size and configuration of their surgical tools and other devices involved. In these systems, each manipulator consists of a surgical tool at one end and a bulky drive mechanism at the other end, and this structure results in physical interference when multiple manipulators are used in close proximity. To avoid such interference, devices are set up so that the manipulators and the endoscope are inserted into the patient's body through separate incisions. In addition, the surgical tools used in the da Vinci<sup>®</sup> system have a diameter as large as 11 mm.<sup>3</sup> Due to these factors, it is impossible to insert the set of manipulators needed for treatment through one small cranial opening. If we try to avoid interference by inserting manipulators through more than one cranial opening, it would be difficult to secure the approach route for each surgical tool, and a wide field of operation would be required. This method, therefore, is not appropriate in the field of neurosurgery,

where avoidance of pressure on tissues is desired.

To realize minimally invasive surgery in the field of neurosurgery, it is thus required to create a system that allows the insertion of an endoscope and multiple surgical tools through one small cranial opening and supports the delicate and accurate manipulation of these tools. With this consideration in mind, we developed the manipulator system "HUMAN".<sup>7</sup> In August 2002, we succeeded in the world's first clinical application of HUMAN in the field of neurosurgery,<sup>8</sup> and so far have used this system in the treatment of four patients.

Based on the concept of minimally invasive surgery in the field of neurosurgery, this paper describes the mechanism of the HUMAN system developed to realize the use in clinical settings. It also reports the results of our study confirming the practical effectiveness of this system in clinical use.

### Minimally Invasive Surgery Using the HUMAN System

The purpose of the HUMAN system is to perform a surgical operation using an endoscope and three manipulators inserted through a cranial opening with a diameter of 10 mm. The target of treatment is a tumor with a volume of about 1 cm<sup>3</sup>. While larger tumors need extensive craniotomy, cases of small tumors in this size range are greatly helped by the use of minimally invasive surgery, which is also effective in the improvement of the patient's quality of life (QOL).

This manipulator is capable of performing more finely controlled motions than the human hand and, thus, realizes more delicate surgical treatment. After further development for practical use, this system may be combined with conventional surgery as an advanced surgical instrument supporting delicate operations in about 30% of cases with malignant brain tumors. It will also enable us to treat small tumors in locations that have been inoperable on with conventional methods as well as to perform precise removal of residual tumors located adjacent to functional areas.

### Mechanism of the HUMAN System

Fig. 1 shows an external view of the HUMAN

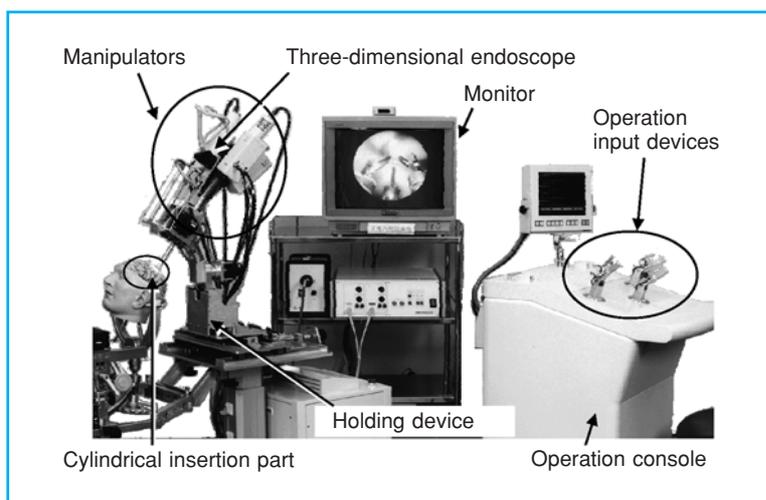


Fig. 1 HUMAN manipulator system

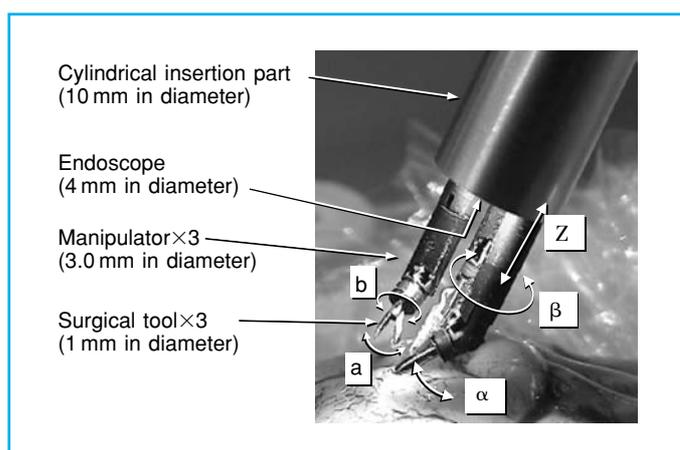


Fig. 2 Magnified image of cylindrical insertion part

system developed by us, and Fig. 2 shows the details of the cylindrical insertion part. While observing the endoscopic image at the center of Fig. 1, the surgeon uses the operation input devices to the right of the figure to perform a surgical operation via the action of the manipulators shown on the left of the figure and in Fig. 2.

The operation input device detects the force applied by the surgeon on the operation lever with a resolving power of 7.8mN. It controls the position of the operation lever in response to the applied force and prevents movement beyond the range of permitted motion.

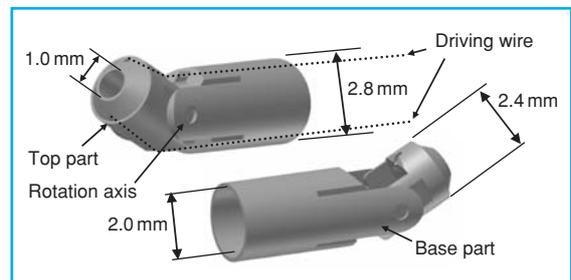
The insertion part (with a diameter of 10 mm)

consists of a bundle composed of an endoscope (4 mm in diameter) and three manipulators (3 mm in diameter). At the tip of each manipulator is a detachable surgical tool (1 mm in diameter). The spaces in the bundle of the manipulators and endoscope contain five irrigation tubes that can be used for dripping and suction. Each manipulator has three degrees of freedom, corresponding to  $\alpha$  (bending),  $\beta$  (rotation), and Z (translation) indicated in Fig. 2. Each surgical tool has a two degrees of freedom, corresponding to a (opening/closing) and b (rotation relative to the joint) in Fig. 2.

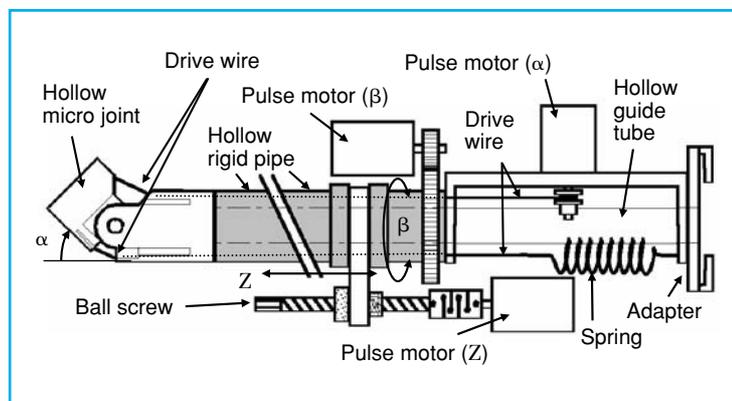
Table 1 summarizes the specification values

**Table 1 Working area and minimum distance**

DOF	$\alpha$	$\beta$	Z
Working area	$1/2\pi$ rad	$2\pi$ rad	50 mm
Minimum distance (designed value)	$8\ \mu\text{m}$ ( $\alpha=0$ rad)	$2\ \mu\text{m}$ ( $\alpha=\pi/2$ rad)	$5\ \mu\text{m}$



**Fig. 3 Hollow micro joint**



**Fig. 4 Drive mechanism of manipulator and micro joint**

for the range of movement (working area) and the smallest step of tool-tip movement (minimum distance) in each direction of the three degrees of freedom. Here, the minimum distance refers to the tool-tip displacement resulting from the one-pulse action of the pulse motor used in the manipulator drive mechanism. Because the minimum distances regarding cocking and rotation depend on the cocking angle at the beginning of movement, the Table gives the values corresponding to the positions where the minimum distance would be the largest.

The manipulator drive mechanism and the endoscope are attached to the holding device via an adapter. The holding device inserts the insertion part into the field of operation in response to the surgeon's manipulation. To ensure safety, insertion is performed with the entire manipulator assembly contained within the insertion part. Manipulators extrude from the insertion part when used in treatment.

Fig. 3 shows the structure of the micro-joint

in the tip of the manipulator. To realize the miniature moving mechanism, a pair of studs on the top (distal) part has been fitted into corresponding holes in the base part to form a rotation axis. The base part and the top part are designed as hollow tubes with the inside diameters of 2 mm and 1 mm, respectively, so that a surgical tool with a diameter of 1 mm can be housed within the joint.

Fig. 4 shows a schematic illustration of the manipulator drive mechanism. The end of a drive wire, connected to the top part of the micro-joint, is connected to the motor controlling the angle of the joint in the  $\alpha$  direction (Fig. 2). This part of the drive mechanism is called the bending unit. Rotation is realized by revolving the hollow rigid pipe together with the micro-joint and the bending unit in the  $\beta$  direction (Fig. 2). Translation is realized by the ball screw producing fine linear motion of the hollow rigid pipe, the bending unit, and the rotation mechanism as a whole in the Z direction (Fig. 2). This structure

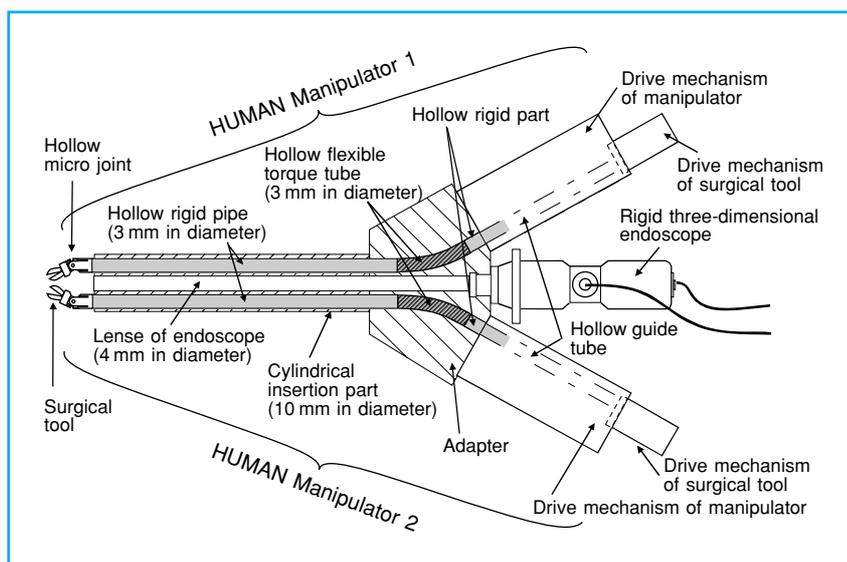


Fig. 5 Structure of thin bundle system

using the nesting of drive mechanisms for different motions ensures freedom from interference between different motions, thereby improving the stability and reliability of movement.

### Thin-bundle System Combining Multiple Manipulators

To be able to operate multiple manipulators as a bundle in the inserted part, interference between manipulator drive mechanisms, as well as that between them and the camera unit of the endoscope, needs to be avoided. A mechanism allowing smooth rotation and translation in the bundle of multiple manipulators is also needed.

In this system, one end segment of the hollow pipe shown in Fig. 4 is made of a hollow flexible torque tube, which is curved and fitted in an adapter so that the drive mechanisms of the multiple manipulators are kept in place without causing mutual interference. Fig. 5 illustrates the system with an endoscope and two HUMAN manipulators installed. This structure solves the problem of interference between mechanical elements. While avoiding interference, the flexible torque tube transmits the torque and thrust for rotation and translation movements along the curved path. When the drive mechanism (shown in Fig. 4; located in an area of the drive

mechanism of the HUMAN manipulator in Fig. 5) exerts the torque and thrust for rotation and translation movements, the action is efficiently transmitted to the joint at the tip of the manipulator.

### Mechanism for Changing Surgical Tools

A surgical manipulator must have a mechanism for changing surgical tools without replacing the manipulator itself so that the development of surgical tools may be facilitated and a variety of surgical tools can be used during an operation.

To create this mechanism for changing surgical tools, we designed the HUMAN system is designed to have a hollow structure as shown in Fig. 4. We developed a surgical-tool unit that enables various surgical tools to be attached to and removed from the tip joint by means of insertion and withdrawal through the bore. We also developed various tools that can be attached and removed in this way; including those with driving mechanisms, such as tweezers, biopsy forceps, scissors, and bipolar forceps,<sup>9</sup> and those without driving mechanisms, such as monopolar tools, S-shaped hooks, spatulas, and needles.

The surgical-tool unit consists of a power-transmission part, with an outside diameter of

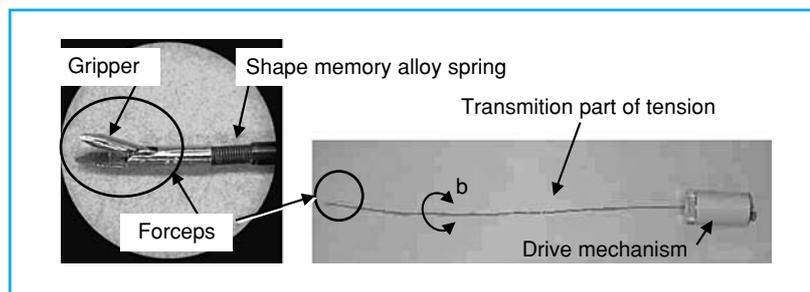


Fig. 6 Surgical-tool unit

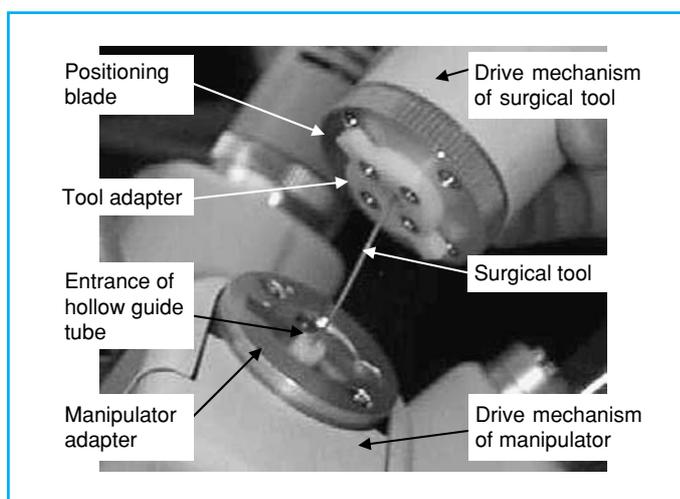


Fig. 7 Usage of exchangeable adapter module

1 mm, which extends from the drive mechanism and has a pair of forceps at the tip (Fig. 6). The opening and closing motions of the gripper part are controlled by transmission of the power produced by the drive mechanism via the drive wire located in the tension-transmission part. A torque tube with high torque-transmission efficiency is used in the tension-transmission part. With this mechanism, the tool inserted in the joint can be rotated (motion labeled “b” in Fig. 2 and Fig. 6) by the twisting motion of the power-transmission part applied to the drive mechanism, and the tool can be inserted and withdrawn freely even when the path in the hollow tube is curved as in Fig. 5. The ability to rotate the surgical tool enables the direction of the opening and closing of the tool to be changed relative to the direction of joint bending ( $\alpha$  in Fig. 2), thereby improving the maneuverability

of treatment operation.

To achieve this rotation capability, the forceps must be able to be bent toward in direction and follow the bending of the joint. To this end, the part corresponding to the movable part of the micro-joint on a neck of the forceps has been designed with a super-elastic shape-memory-alloy spring (Fig. 6). This super-elastic material has the advantage of high flexibility combined with the resistance to plastic deformation. Irrespective of the direction of the opening and closing of the tool relative to the bending direction of the joint, this structure of forceps enables the surgical tool unit to follow the bending motion of the manipulator without interference. At the same time, this structure with a shape-memory-alloy spring prevents permanent curling of the device in a certain direction, realizing a durable system suitable for practical use.

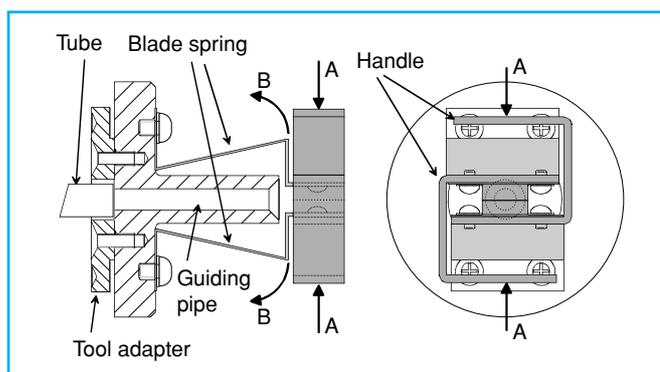


Fig. 8 Tool holder

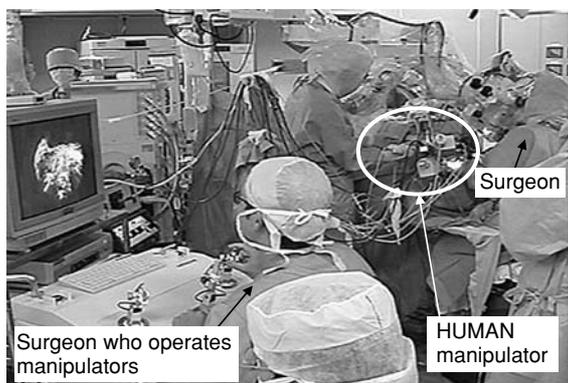
Fig. 7 illustrates how the surgical unit is installed. The surgical tool is fixed to the manipulator by a newly developed adapter module consisting of a tool adapter and a manipulator adapter complementing it. The tool adapter is fixed to the end of the surgical-tool drive mechanism (Fig. 7). The manipulator adapter is fixed to the bending unit (to the extreme right in Fig. 4 and in Fig. 7). At the center of this adapter, there is an entrance leading to the bore of the manipulator. The surgical tool is inserted from here and is led through the hollow path to the joint tip. The tool adapter is then connected to the manipulator adapter using a rotating motion, which integrates the tool and manipulator drive mechanisms. This connection also integrates the inserted tool with the micro-joint as shown in Fig. 2. Similarly to the structure shown in Fig. 4, this structure avoids mutual interference between different motions of the manipulator and the surgical tool, realizing good stability and reliability of motions during use of the manipulator with surgical tools attached.

Fig. 8 schematically shows the surgical-tool holder, which is used for attaching monopolar forceps and other dedicated tools with no drive mechanism, as well as third-party flexible surgical tools, to the manipulator. Also attached to this holder is a tool adapter that can be attached to the manipulator drive mechanism in place of the tool drive mechanism. The surgical tool is inserted into the guiding pipe connected to the bore of the manipulator, and this tool is held by handles. As an example, we experimentally confirmed the feasibility of this holder in using third-party optical fibers for laser knives.<sup>10</sup>

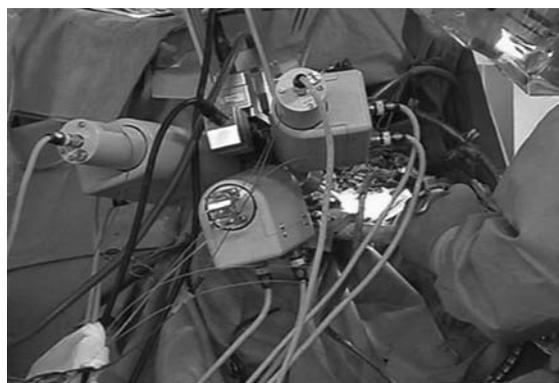
### Safety Control

Because conventional systems are targeted at use in the abdominal cavity, they are designed to move the manipulator over a wide area with a spatial resolution of several millimeters. In the position-control systems developed for such applications, the position of the operating lever responding to the surgeon's maneuver is sampled at a frequency of 1,000 times per second and feedback to the manipulator.

In contrast, because our system is intended for neurosurgery, it can perform fine movements at steps smaller than  $10\ \mu\text{m}$  in volumes as small as  $1\ \text{cm}^3$ , as shown in Table 1. It detects the input force applied by the surgeon at a frequency of 250 times per second and with a resolving power of 7.8 mN. According to the detected amount of input movement, the position after the execution of movement is calculated and actual movement is performed only when the calculated result falls within the prescribed range of allowed movement. This method of control, developed for this system to ensure safety, is called "prior-confirmation-based safety control". Compared with frequency of position detection of conventional systems, that of our system is lower, but a higher degree of safety is realized, because safety is confirmed before actual movement and the resolving power is finer than that of conventional systems by a factor of 100. In this way, our system prevents any movement of the manipulator beyond the predetermined range in the field of neurosurgery, where the safety of the surrounding normal tissues is crit-



**Fig. 9 Clinical use of the HUMAN system (overall view)**



**Fig. 10 Clinical use of the HUMAN system (close-up)**

ical. In this system, the check and control for ensuring the safety of manipulation in the background of operation is performed in a triplicate manner.

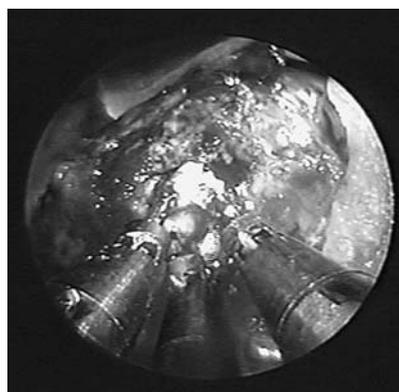
### Clinical Use

In addition to the mechanical development described above, we have repeated manipulation experiments,<sup>10–12</sup> confirmed sterilization properties,<sup>13</sup> and simulated surgical operations<sup>14</sup> in cooperation with surgeons.

This system was designed as a unit-based structure that can be disassembled and assembled by medical staff, and all parts were sized to fit in sterilization containers, ensuring the ease of sterilization and scrubbing. In the sterilization experiments, all separable units of the manipulator system were treated with ethylene oxide gas (EOG) sterilization, and we confirmed that the number of viable bacterial cells was  $10^{-6}$  times lower than the level needed to guarantee sterility. In the manipulation experiments and the simulated surgical operations using our system, presuming actual surgical operations, we repeatedly evaluated the methods of system operation and confirmed the surgical procedures.

After these experiments, we obtained the approval of the ethics committee of Shinshu University and the informed consent from patients and their families. Following these steps, we have so far been able to use this system in the treatment of four patients.

The first clinical use of this system was as represented in Fig. 9 to Fig. 11. The patient was a



**Fig. 11 Endoscopic view of manipulators performing enucleation of a tumor**

54-year-old male. The target lesion was a recurrent meningioma in the left middle cranial fossa.<sup>8</sup> In this clinical case, conventional craniotomy was performed, and the manipulator was set up at the side of the surgeon performing the operation with his own hands. Another surgeon operated the manipulator, while observing the field of operation in the endoscopic image, as shown in Fig. 11. Procedures performed using the manipulator started with the separation of normal brain tissues and tumor by using a spatula and an S-shaped hook. Detachment was performed by grasping the tissues with forceps. Next, bipolar forceps were used to coagulate blood vessels on the tumor surface, and the tumor was exposed and then enucleated using a laser knife and forceps. The time required for tool exchange and resuming the operation was

about 1 min per exchange.

During the operation, smoke resulting from the use of the laser knife and bipolar forceps, as well as fogging and staining of the endoscope lens, was generated. However, a clear field of view could be maintained throughout the operation by smoke suction and dripping via the irrigation tubes installed in the insertion part.

As shown in Fig. 11, the system can safely remove a tumor as small as about 1 mm using the finely controlled movement of the manipulator. According to the system warning, input operations exceeding the prescribed limits of motion occurred during the operation, but the prior confirmation-based safety control worked and the manipulator did not move beyond the range of permitted motion.

## Discussion

Conventional systems are designed to work in wide spaces in the peritoneal cavity, and treatment using such systems is set up with two manipulators (10 mm in diameter) and an endoscope inserted through three incisions. In this case, the manipulators move widely to cover the wide area to be treated. Collision between the arms holding the manipulators, as well as collision between a manipulator and a medical staff nearby, occasionally takes place, so medical staffs have to pay great attention to manipulators when supporting treatment around them.

In contrast, our system (with a thin bundle system structure) enables three manipulators (3 mm in diameter) and an endoscope to approach the lesion through a single insertion part (10 mm in diameter). In addition, it can perform fine movement of manipulators without moving the insertion part. As a result, this system also opens up the possibility of cooperative treatment in which a manipulator system is set up next to a surgeon performing delicate treatment. In these respects, our system is considered safer and more convenient than conventional systems using large motions.

Conventional systems have already been provided with interchangeable dedicated surgical tools. However, it has been demonstrated in clinical tests that the HUMAN system can be used with third-party surgical tools, such as optical fibers for laser knives, in addition to dedicated tools. The ability to accept third-party surgical

tools means wider choices of surgical tools to meet various clinical situations. In addition, the HUMAN system accepts almost any surgical tool that has an outside diameter of no more than 1 mm and is flexible. This advantage encourages the development of surgical tools in response to the needs in clinical practice and, thus, helps increase system expandability. Through the training effect, it is considered possible to shorten the time required for changing surgical tools and resuming the operation procedure.

The use of fine movements smaller than 10  $\mu\text{m}$  was infrequent, but the movements were effective in situations requiring careful manipulation, such as manipulation around a tumor. Since movement beyond the range of permitted motion was successfully prevented in clinical use, the ability to achieve fine movement and the prior-confirmation-based safety control contributed synergistically to the improvement of safety.

As discussed above, the practical feasibility of the basic functions of the HUMAN system has been confirmed in clinical settings.

## Conclusion

We developed a surgical manipulator system—called HUMAN—to enable minimally invasive surgery in the field of neurosurgery. This system is characterized by the concept of performing minute and accurate surgical manipulation using an endoscope and three surgical tools inserted through a single small cranial opening. As a world's first, we succeeded in the clinical application of a manipulator system to the field of neurosurgery and confirmed the practical feasibility and safety of this system.

As a characteristic feature of this system, a manipulator incorporating a flexible-torque-tube structure, which consists of three surgical tools and an endoscope contained in the insertion part with a diameter of 10 mm, was first developed. Next, stable movement of this system with surgical tools installed in the insertion part was achieved. This made it possible to perform minimally invasive surgery via a single insertion part. We conducted clinical tests using the manipulator system at the side of a surgeon. These tests demonstrated that the surgeon and the manipulator system can cooperate and safely perform therapeutic operations.

Second, a mechanism for easy replacement

of surgical tools, as well as a large variety of surgical tools that can be attached to the manipulator, was developed. We demonstrated the convenience and practical effectiveness of this mechanism in clinical tests, where we were able to use and replace multiple surgical tools (including forceps and laser knives) as needed during a surgical procedure.

With respect to system safety, we developed a drive mechanism to avoid interference between different motions of a manipulator. As a result of this mechanism, high performance, namely, minute therapeutic manipulation smaller than 10  $\mu\text{m}$ , was achieved. We also developed a method called “prior-confirmation-based safety control”, in which actual movement of the manipulator takes place only after prior calculation of the position that would result from the input manipulation. These two mechanisms realized a high degree of safety in a field of application,

such as the field of neurosurgery, where ensuring the safety of the surrounding normal tissues is critically important. At the same time, the results of our clinical trial demonstrated the ability of these mechanisms to support the safe operation of the system in clinical use. In future development of the HUMAN system, we plan to expand its applicability to a larger variety of cases and more fields of practice.

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# An Analysis of Ambulance-transported Cases of Attempted Suicide in 3 Prefectures (Akita, Aomori, and Iwate) in the Northern Tohoku Area in Japan

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Chikara Yonekawa,\*<sup>1</sup> Hajime Nakae,\*<sup>2</sup> Kimitaka Tajimi,\*<sup>2</sup> Yutaka Motohashi,\*<sup>3</sup> Yasushi Asari,\*<sup>4</sup> Shigeatsu Endo,\*<sup>5</sup> Sergio A Perez Barrero\*<sup>6</sup>

## Abstract

A survey was conducted on the 2,556 patients who attempted suicide and were transported via ambulance during the period from 2003 to 2004 in 3 prefectures in the northern Tohoku area. The mean age of the patients was  $47.2 \pm 19.1$  years ( $49.3 \pm 17.8$  for males and  $44.8 \pm 20.3$  for females). The most common method of suicide was by hanging (261 cases in Akita, 229 in Aomori, and 312 in Iwate), followed by overdosing and self harm by means of cutting or stabbing. Depression was the most common underlying mental disorder (116 cases in Akita, 95 in Aomori, and 91 in Iwate), followed by schizophrenia, neurosis, and psychogenic reaction. The method of suicide resulting in the highest death rate was by hanging (74.9% in Akita, 68.8% in Aomori, and 68.8% in Iwate). Public education and other actions in society at large are essential for the prevention of suicide. Considering the need for detecting a depressive state foreboding suicide attempts and also for preventing repeated attempts, both psychiatrists and primary physicians in the community should be proactively involved in the issue of suicide.

**Key words** Suicide, Northern Tohoku, Suicide prevention

## Introduction

In September 2004, the World Health Organization (WHO) alerted the world with the message stating: “Suicide is a huge but largely preventable public health problem, causing almost half of all violent deaths and resulting in almost one million fatalities every year, as well as economic costs in the billions of dollars.” Japan has also been experiencing a rapid increase in deaths from suicide since 1998.<sup>1</sup> Three prefectures

in the northern Tohoku area (Akita, Aomori, and Iwate) have been recording particularly high suicide death rates. The rates per 100,000 population in 2004 were 39.1 in Akita, 38.3 in Aomori, and 34.6 in Iwate.<sup>1</sup> These statistics refer to deaths from suicide, and there are actually many more cases of attempted suicide. We previously conducted a questionnaire survey with fire departments in Akita prefecture and reported the occurrence of suicide attempts in the prefecture.<sup>2</sup> Expanding this study approach, we next conducted a study covering the 3 pre-

\*1 Internal Medicine Department, Municipal Ugo Hospital, Akita; \*2 Division of Emergency and Critical Care Medicine, Department of Integrated Medicine, Akita University School of Medicine, Akita; \*3 Division of Public Health, Department of Social Medicine, Akita University School of Medicine, Akita; \*4 Emergency and Disaster Medicine, Hirosaki University School of Medicine, Hirosaki; \*5 Department of Critical Care Medicine, Iwate Medical University, Morioka; \*6 Temporary Adviser of OPS/OMS for the Prevention of the Suicide in The Americas Miembro of IAPS, IASR, AITS, BI, GEPS, ASULAC

Correspondence to: Chikara Yonekawa MD, Internal Medicine Department, Municipal Ugo Hospital, 44-5 Aza-Odomichi, Nishimonai, Ugo-machi, Akita 012-1131, Japan. Tel: 81-183-62-1111, Fax: 81-183-62-3174, E-mail: yone-c@sc4.so-net.ne.jp

**Table 1** Number of suicides, suicide rate, and mean age in 3 prefectures in northern Tohoku (Akita, Aomori, and Iwate)

		Suicides	Suicide rate (per 100,000 pop.)	Age (Years)	
Akita	M	418	38.3	49.4 ± 17.5	] $P=0.0241$
	F	362	29.6	46.4 ± 20.5	
	Total	780	33.7	48.0 ± 19.0	
Aomori	M	428	31.7	48.8 ± 17.9	] $P<0.0005$ n.s.
	F	382	25.1	44.2 ± 19.7	
	Total	810	28.1	46.7 ± 18.9	
Iwate	M	518	39.3	49.6 ± 18.1	] $P<0.0001$ n.s.
	F	448	31.2	44.1 ± 20.6	
	Total	966	34.7	47.0 ± 19.5	
Total of 3 prefectures	M	1,364	36.3	49.3 ± 17.8	] $P<0.0001$
	F	1,192	28.5	44.8 ± 20.3	
	Total	2,556	32.2	47.2 ± 19.1	

fectures in the northern Tohoku area, where the problem of suicide is particularly remarkable among the regions in Japan. We examined the characteristics of ambulance-transported cases of suicide attempts in the 3 prefectures, and provided some discussion concerning the measures for preventing suicide.

### Subjects and Methods

Fire departments in Akita, Aomori, and Iwate prefectures (43 departments in total) were asked to participate in the questionnaire survey. The scope of study was the period of 2 years from January 1, 2003 to December 31, 2004. Information concerning age, sex, injury (method, place, and time), presence or absence of mental disorders, and the fatality of the act was collected. As for the definition of suicide, cases satisfying at least one of the following criteria from 1) to 4) were considered to have attempted suicide: 1) The patient stated that he/she had attempted suicide. 2) There was a suicide note or the patient had given an advance notice of death. 3) There was a witness observing the conduct of the act of suicide. 4) Although none of the above was noted, the mechanism of injury was unnatural in view of the situation and at least 2 of the following conditions were observed: (1) the patient had suicidal tendencies; (2) the patient had a history of suicide attempts; (3) the

patient had a history of mental illness, the patient was receiving treatment for mental illness, or another person testified the presence of obvious mental symptoms; and (4) there was a clear trigger or a definite motive.

According to ICD-10, the method of suicide attempt was classified into (1) to (11) as follows: (1) drugs, (2) pesticides, (3) gassing, (4) jumping in front of a moving vehicle, (5) jumping from height, (6) cutting and stabbing, (7) hanging, (8) drowning, (9) firearms, (10) self-burning, and (11) other. Mental disorders were diagnosed at the hospital accepting the patient, and were classified into (1) to (7) below according to DSM-IV: (1) schizophrenia, (2) manic-depressive psychosis, (3) neurosis and psychogenic reaction, (4) toxic psychosis and substance dependence, (5) epilepsy, (6) organic brain syndrome, (7) other.

In some cases, additional information concerning the course of treatment was obtained through hearing from the hospitals accepting the patients. Due attention was paid in this process to ensure the protection of the patient's privacy.

The data were expressed as mean ± S.D. Statistical analyses were based on the Student's *t*-test for comparison between 2 groups and the  $\chi^2$  independence test for comparison among 3 prefectures. A difference with  $P<0.05$  was considered significant.

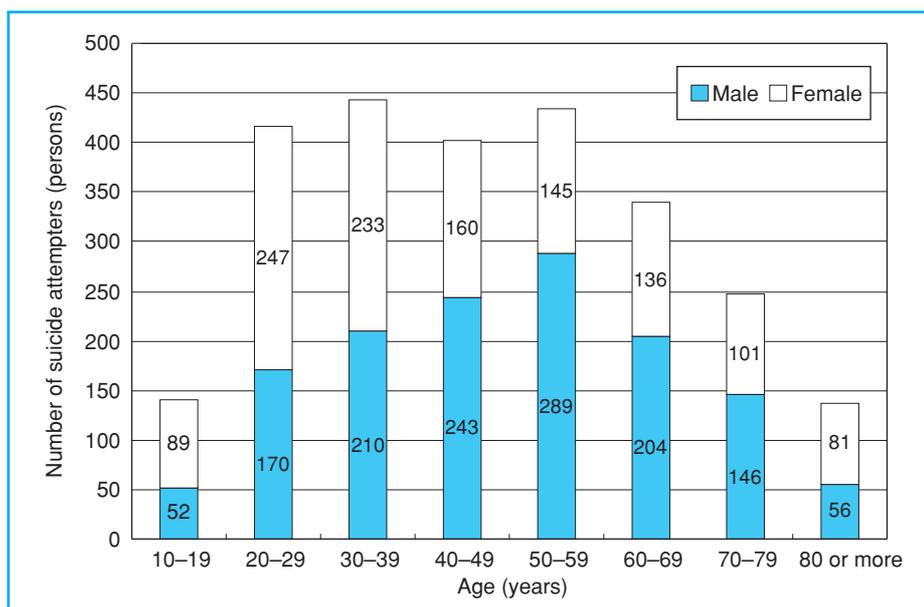


Fig. 1 Number of suicide attempters in the 3 prefectures in northern Tohoku (2003–2004)

## Results

Answers were obtained from all 43 fire departments.

### Cases

There were 2,556 cases identified in this study (1,364 males and 1,192 females). The mean age of all cases was  $47.2 \pm 19.1$  years:  $49.3 \pm 17.8$  for males and  $44.8 \pm 20.3$  for females. The mean age of male cases was significantly higher than that of female cases ( $P < 0.0001$ ). All 3 prefectures showed the same tendency in this respect (Table 1). The rate of suicide attempt cases per 100,000 population was 33.7 in Akita, 28.1 in Aomori, and 34.7 in Iwate (Table 1). The age distribution showed a peak in the 40–59 age bracket among males and in the 20–39 age bracket among females (Fig. 1).

### Method of suicide

Hanging was the most common method of suicide in all prefectures, followed by drugs and then by cutting and stabbing (Fig. 2).

### Disease classification

The percentage of cases diagnosed as having men-

tal illness at initial examination was 34.43% in Akita, 24.11% in Aomori, and 30.15% in Iwate, and the differences were significant ( $P < 0.0001$ , Table 2). Depression was the most frequent diagnosis (42.9% in Akita, 47.9% in Aomori, and 30.9% in Iwate), followed by schizophrenia (7.7% in Akita, 8.0% in Aomori, and 11.9% in Iwate) and neurosis (11.4% in Akita, 5.0% in Aomori, and 8.1% in Iwate). These represented more than a half of all cases (Fig. 3).

### Death rate

The death rate among suicide attempters was 34.5% in Akita, 35.5% in Aomori, and 39.7% in Iwate, and the differences were significant ( $P = 0.0471$ ). As seen by the method of suicide, the death rate was overwhelmingly high with hanging (74.9% in Akita, 68.8% in Aomori, and 68.8% in Iwate), followed by gassing (11.1% in Akita, 10.3% in Aomori, and 14.2% in Iwate). The rates associated with other methods remained in the range of several percent.

### Occurrence by the hour of the day and by the month

The occurrence of suicide attempts by the hour of the day started to increase at 6 a.m., corresponding to the increased activity of people, and

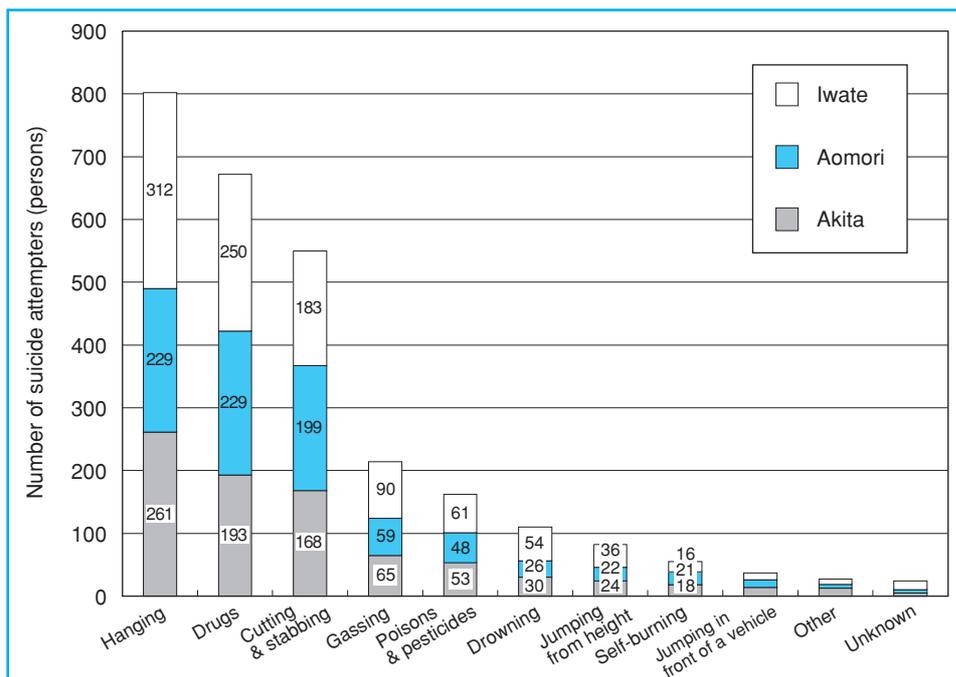


Fig. 2 Methods of suicide used by suicide attempters in the 3 prefectures in northern Tohoku (2003–2004)

Table 2 Suicide deaths, death rate, number and percentage of cases with mental disorders, and involvement of alcohol in 3 prefectures

	Suicide deaths	Suicide death rate (%)	Cases with mental disorders	Mental disorders/suicide attempts (%)	Alcohol involved (persons)	Alcohol involved (%)
Akita	271	34.5	270	34.43	109	13.9
Aomori	292	35.5	198	24.11	67	8.16
Iwate	388	39.7	294	30.15	104	10.6
$\chi^2$ test		$P=0.0471$		$P<0.0001$		$P=0.0013$

was low during the period after 20:00, at midnight, and before dawn. As seen by the month, there were about 70 cases of suicide attempts in each month, showing no accumulation in particular months.

### Involvement of alcohol

The percentage of suicide attempters using alcohol in some form before the conduct was 13.9% in Akita, 8.16% in Aomori, and 10.6% in Iwate, and the differences were significant ( $P=0.0013$ , Table 2).

### Discussion

Suicide is a major social problem. While the annual number of deaths from suicide in Japan has remained around 30,000 for several years, 3 prefectures in the northern Tohoku area (Akita, Aomori, and Iwate) have been ranked high in the suicide death rate for 3 years since 2002. According to the Vital Statistics of Population, the suicide rate per 100,000 population in 2004 was 39.1 in Akita, 38.3 in Aomori, and

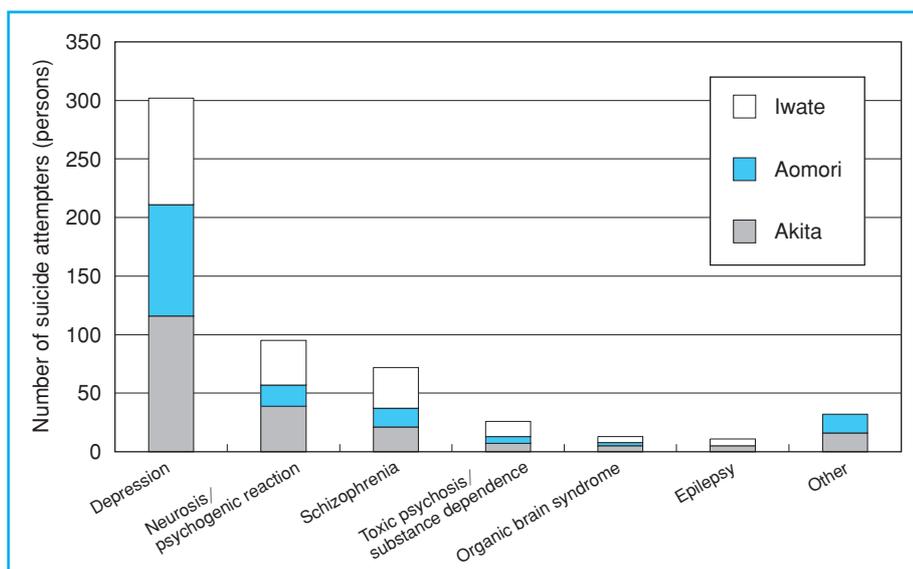


Fig. 3 Disease classification of suicide attempters with mental disorders in the 3 prefectures in northern Tohoku (2003–2004)

34.6 in Iwate.<sup>1</sup> In the present study, the suicide rate was lower than the suicide death rate presumably because the study covered only the cases that were ambulance-transported after suicide attempts. The age distribution of suicide attempters showed a peak in the 40–59 age bracket among males and in the 20–39 age bracket among females. Although the peak in the age distribution of suicide was observed in the older age bracket in the past, the peak is now tending to move toward younger ages. While depression has been identified as a risk factor responsible for the high suicide rate among aged persons,<sup>3</sup> recent tendencies suggest the increase in young and middle-aged persons who attempt suicide because of economic hardships of life resulting from unemployment and prolonged recession, as well as the increase in young persons committing suicide because of difficulty in solving human relation problems.

The most common method of suicide was by hanging, as is the case in the national statistics.<sup>1</sup> Suicide by hanging tends to be conducted impulsively, because it can be done without special preparation. When death rates were compared by the method of suicide, hanging resulted in the death of the person at an overwhelmingly higher rate than other methods. This may be explained by the fact that suicide by hanging is

usually conducted in concealed places and a long period of time is elapsed before discovery. Therefore, it is important to take care so that a person showing signs of suicide should not be left alone. Although jumping from height is the 2nd most common method of suicide in Japan, this method was rare in this area, reflecting the scarceness of high-rise buildings in the 3 prefectures in the northern Tohoku area.

About 30% of the cases had mental disorders, and the most common underlying disorder was depression. A survey conducted overseas has shown that 90% of the cases examined at hospitals after suicide attempts had at least one mental disorder, and a majority of them had depression.<sup>4</sup> Generally speaking, many suicide attempters are in a psychological condition such as a depressive state before committing suicide, often accompanied by loss of appetite, insomnia, and general deterioration of physical condition. Persons who are going to commit suicide often visit medical services such as internal medicine clinics because of this reason,<sup>5</sup> and hence there is a need for intervention to prevent suicide at this stage, i.e., treatment of depression. Despite this need, the 3 prefectures in the northern Tohoku area are not provided with a sufficient number of physicians, and the availability of medical services is unevenly concentrated in

urban areas. In addition, initial care for the patients attempting suicide is mostly provided by general internists and surgeons rather than psychiatrists. In this respect, actions should be taken to disseminate the knowledge concerning the nature and treatment of depression to general physicians, who are likely to take part in emergency medicine.

In the present study, the use of alcohol in some form was associated with suicide attempts in about 10% of cases. Since Borges et al.<sup>6</sup> reported that 35% of cases consumed alcohol within 6 hours before suicide attempts, the actual rate of alcohol use in our study might have been much higher than reported. While a moderate drinking habit does not affect the mortality index, heavy drinking has been associated with a significantly high occurrence of deaths from suicide.<sup>7</sup> The fact that the 3 prefectures in the northern Tohoku area are ranked the highest in the men's drinking index among the prefectures in Japan<sup>8</sup> suggests the possibility that the high prevalence of a drinking habit may be contributing to the high suicide rate. Therefore, improvement of drinking habits is also essential for the prevention of suicide.

Although Akita prefecture remains in the

dishonorable position of recording the highest suicide rate in Japan, efforts to reduce suicide have been continued, including meetings involving not only psychiatrists, but also persons from various fields, and the suicide prevention campaign starting in 2001 resulted in a 27% decrease in the suicide rate for 3 years. The number of deaths from suicide has also decreased in 2 successive years. However, it is undeniable that the number of suicides is still high. While suicide prevention should be achieved through the 3 stages of prevention, intervention, and postvention, the role of emergency medicine mostly resides in the intervention stage. The ongoing efforts toward effective suicide prevention require activities to educate the general public, to improve the understanding and recognition of suicide on the part of health care workers, and above all, to provide guidance and treatment for potential suicide attempters.

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# Gender Differences in Symptom Experience at End-of-Life among Elderly Patients Dying at Home with Advanced Cancer in Japan

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Yoshihisa Hirakawa,\*<sup>1</sup> Yuichiro Masuda,\*<sup>1</sup> Masafumi Kuzuya,\*<sup>1</sup>  
Akihisa Iguchi,\*<sup>1</sup> Kazumasa Uemura\*<sup>2</sup>

## Abstract

**Background** It is unclear whether gender differences exist among elderly patients dying at home with advanced cancer in terms of symptom experience and care receipt at end-of-life. The aim of the present study is to determine the gender-specific features in symptom experience in the last days of life with distinction of age (65 and over).

**Methods** We conducted a sub-analysis study of the Dying Elderly at Home (DEATH) project, a multicenter study of 240 elderly patients dying at home. We assessed the frequency of symptoms and end-of-life care receipt in elderly patients dying at home during the last two days of their lives in order to evaluate the differences observed between the two gender groups. A total of 52 female and 65 male decedents were included in the analysis.

**Results** Female decedents experienced coma more frequently than male decedents, but the opposite was true of sputum. There were no significant differences in all care options between the two groups. After controlling for age, ADLs, cognitive impairment, and cause of death, gender was determined to be a significant independent predictor of nausea/vomiting and sputum.

**Conclusions** This study suggests that consideration should be given to gender differences in symptom experience and management at end-of-life.

**Key words** Opioid, Terminal care, Death, Pain, QOL

## Introduction

The growth of the aging population in Japan has triggered an increase in the demand for end-of-life care for the elderly dying with cancer.<sup>1</sup> In advanced cancer, when cure is impossible, symptom management should be the focus of attention. A better understanding of symptom experience of such patients would be useful for counseling patients and families and better designing programs, such as home benefits, to care for patients at the end of life.

A number of studies have suggested that there may be differences in symptom experience among men and women cancer patients.<sup>2–4</sup> Thus, the application of gender-specific information on elderly symptom experience at end-of-life may improve the quality of life of all elderly cancer patients.

However, it remains unclear whether gender differences exist because this topic has not yet been widely investigated. A few studies have reported no gender differences in symptom experience,<sup>5,6</sup> while other studies have suggested the existence of age-related differences in symptom experi-

\*1 Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya

\*2 Center of Medical Education, Nagoya University School of Medicine, Nagoya

Correspondence to: Yoshihisa Hirakawa MD, PhD, Department of Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. Tel: 81-52-744-2364, Fax: 81-52-744-2371, E-mail: y.hirakawa@k8.dion.ne.jp

ence.<sup>3,5,7-9</sup> In order to investigate the gender-specific features in symptom experience of elderly cancer patients in the last days of life with distinction of age (65 and over), we conducted a sub-analysis study of the Dying Elderly at Home (DEATH) project. This is a prospective observational study of two hundred and forty community-dwelling elderly dying at home in Japan. Because in recent years a growing number of elderly people chose to spend the last years of their lives at home,<sup>10-12</sup> home death has been the focus of increasing attention.<sup>13</sup>

Our results motivated us to make a recommendation for the development of appropriate end-of-life care plans for male and female elderly patients in community settings.

## Methods

### Study design and population

The present data was obtained from the Dying Elderly at Home (DEATH) project, a multicenter observational study. The DEATH project was conducted in collaboration with the Japanese Society of Hospice and Home-care. The society is a non-profit organization consisting of general physicians and other medical and social professionals interested in hospice and home-care. Two hundred and forty decedents aged 65 or older who were using 16 study clinics belonging to the society with diagnoses of all illnesses including advanced cancer and who died at home from October 2002 to September 2004 were included in the study. Decedents were excluded if they were transferred to a hospital at death. The following information was collected: sociodemographics, ADLs (Japan's Ministry of Welfare identifies four ranks of ADL of disabled elderly as follows<sup>14</sup>: Rank J (independent in ADLs), Rank A (house-bound), Rank B (chair-bound), and Rank C (bed-ridden), cognitive impairment, observed symptoms and provided end-of-life care during the last 48 hours of their lives. Symptom experience was assessed based on our original questionnaire focusing on the following twenty symptoms, which represent common symptoms among elderly patients at the end of life. Thus, we did not hypothesize that there are gender differences in experience of the symptoms. With the approval of the Japanese Society of Hospice and Home-care, we used a questionnaire that included a list of common symptoms and treatments at the

end-of-life as follows:

### Symptoms

Dyspnea, uncontrolled pain, controlled pain, coma, acute confusion, anxiety, dizziness, nausea and vomiting, anorexia, diarrhea, constipation, fever, urinary and fecal incontinence, hematemesis, hemoptysis, bottom blood, other types of hemorrhage, cough, sputum, and others.

### End-of-life care

Heart massage, intubation, mechanical ventilation, oxygen inhalation, air-way placement, sputum suction, hyperalimentation, intravenous drip injection (except hyperalimentation), antibiotics, vasopressor, blood transfusion, opioids, urinary catheter placement, mental support, spiritual healing, others.

### Data collection

Immediately after the death of study patients, general practitioners (GPs) were asked to fill out a questionnaire based on the patients' medical charts and their recollection of the clinical course followed. Family members or visiting nurses who witnessed the last 48 hours of the patients' lives were asked to provide additional information. The GPs and other information providers were blinded to the study hypothesis or anticipated study results. For ethical reasons, data on all eligible participants obtained from the Japanese Society of Hospice and Home-care remained anonymous. The research protocol was reviewed and approved by the Nagoya University Research Ethics Board.

### Statistical analysis

We used the DEATH sample data of all decedents whose cause of death was any type of cancer, with or without metastasis. Decedents who were diagnosed with cancer but did not die of it were not included in the analysis. Thus, a total of 52 female and 65 male decedents were included in the analysis. To assess the differences in characteristics and symptom experience among female and male decedents, the survey data was divided into two gender groups. The data was analyzed using Statview-J5.0. Group differences were compared using the unpaired *t*-test and the chi square test. *P* values <0.05 were considered to be significant. We also performed a multivariable logistic regression analysis to identify any independent association between gender group and symptom, after adjusting for baseline

factors. As predictors of symptoms, age, ADLs, cognitive impairment, and cause of death were allowed to enter the model. We present the results as odds ratios and 95% confidence intervals.

## Results

The distribution of female and male cancer decedent characteristics is shown in Table 1. Most female decedents were significantly older than their male counterparts. Furthermore, cognitive impairment was more common among female

decedents. There were no significant differences in ADLs, cause of death, or complicated illness between female and male decedents.

Female and male cancer decedents' symptom experience in the last two days of life is shown in Table 2. Coma was more frequent among female decedents, while sputum was more common among male decedents. Although nausea and vomiting tended to be frequent among female decedents, we detected no significant difference in nausea and vomiting between the two groups. There were no significant differences in the fre-

**Table 1 Characteristics of male vs female elderly cancer decedents**

Variable	Women (n = 52)		Men (n = 65)		P	
	n/average	%/SD	n/average	%/SD		
Age	76.42	1.32	73.17	1.05	0.05	
ADL scale of disabled elderly	J = independent	1	1.92	1	1.54	0.76
	A = house-bound	4	7.69	7	10.77	
	B = chair-bound	10	19.23	16	24.62	
	C = bed-bound	30	57.69	29	44.62	
	Unknown	7	13.46	12	18.46	
Cognitive impairment	Present	17	32.69	10	15.38	0.03
Cause of death (primary sites)	Gastric	9	17.31	19	29.23	0.47
	Lung	12	23.08	15	23.08	
	Liver	3	5.77	5	7.69	
	Colorectal	6	11.54	8	12.31	
	Pancreas	3	5.77	4	6.15	
	Prostate	0	0.00	6	9.23	
	Breast	2	3.85	0	0.00	
	Kidney	1	1.92	2	3.08	
	Uterine	3	5.77	0	0.00	
	Blood	0	0.00	0	0.00	
	Brain	0	0.00	0	0.00	
	Others	8	15.38	5	7.69	
	Unknown	5	9.62	1	1.54	
	Complication (noncancer illness)	Pulmonary	3	5.77	5	
Cardiovascular		3	5.77	1	1.54	0.23
Cerebrovascular		2	3.85	2	3.08	0.82
Kidney		1	1.92	0	0.00	0.26
Liver		5	9.62	6	9.23	0.94
Gastrointestinal		2	3.85	0	0.00	0.11
Others		10	19.23	3	4.62	0.01
Unknown		1	1.92	1	1.54	0.87

ADL: activity of daily living

**Table 2 Symptom experience of male vs female elderly cancer decedents in last two days of life**

Symptom	Women (n=52)		Men (n=65)		P
	n	%	n	%	
Dyspnea	22	42.31	34	52.31	0.28
Pain (uncontrolled)	13	25.00	12	18.46	0.39
Pain (controlled)	23	44.23	35	53.85	0.30
Coma	31	59.62	20	30.77	<0.01
Acute confusion	14	26.92	12	18.46	0.27
Anxiety	5	9.62	9	13.85	0.48
Dizziness	1	1.92	1	1.54	0.87
Nausea and Vomiting	19	36.54	14	21.54	0.07
Anorexia	29	55.77	42	64.62	0.33
Diarrhea	3	5.77	4	6.15	0.93
Constipation	5	9.62	4	6.15	0.49
Fever	12	23.08	18	27.69	0.84
Incontinence	9	17.31	9	13.85	0.60
Hematemesis	1	1.92	3	4.62	0.43
Hemoptysis	0	0.00	1	1.54	0.37
Bottom blood	2	3.85	5	7.69	0.38
Other hemorrhage	2	3.85	7	10.77	0.16
Cough	6	11.54	9	13.85	0.71
Sputum	10	19.23	25	38.46	0.02
Other symptom	12	23.08	17	26.15	0.70

**Table 3 Care receipt of male vs female elderly cancer decedents in last two days of life**

Care	Women (n=52)		Men (n=65)		P
	n	%	n	%	
Heart massage	0	0.00	1	1.54	0.37
Intubation	0	0.00	0	0.00	—
Mechanical ventilation	0	0.00	0	0.00	—
Oxygen inhalation	21	40.38	24	36.92	0.70
Airway placement	1	1.92	2	3.08	0.69
Sputum suction	11	21.15	18	27.69	0.42
Hyperalimentation	5	9.62	9	13.85	0.48
Antibiotics	3	5.77	8	12.31	0.23
Vasopressor	0	0.00	0	0.00	—
Blood transfusion	0	0.00	0	0.00	—
Intravenous drip injection	16	30.77	22	33.85	0.72
Opioids	24	46.15	37	56.92	0.25
Urinary catheter placement	13	25.00	10	15.38	0.19
Mental support	0	0.00	3	4.62	0.12
Religious healing	1	1.92	1	1.54	0.87
Others	2	3.85	7	10.77	0.16

quency of pain and acute confusion, either.

Female and male decedents' care receipt in the last two days of life is shown in Table 3. As for care receipt, there were no significant differences in all care options between the two groups.

Multiple regression analysis was carried out to systematically examine the relationships between gender and symptom experience while controlling for predictors of outcome: age, ADLs, cognitive impairment, and cause of death. The unadjusted and multivariable-adjusted results of symptom experience are shown in Table 4. In the univariable analysis, female decedents had a higher experience rate of coma and a lower rate of sputum than male decedents. However, after controlling for age, ADLs, cognitive impairment, and cause of death, being female was determined to be a significant independent predictor of nausea/vomiting and sputum, with an adjusted odds ratio of 3.95 (95% CI, 1.22–12.79) and 0.24 (95% CI,

0.07–0.81) respectively.

## Discussion

Using data from this multicenter, prospective and observational study sample of decedents aged 65 and older regarding symptom experience and care receipt in end-of-life at home, we examined gender differences in symptom experience among elderly patients dying at home. Our study revealed gender differences in terms of symptom experience. Our findings also confirmed that end-of-life care receipt of female and male elderly decedents was comparable. These results support the validity of our study because the symptom experience of advanced cancer elderly patients is related to end-of-life care receipt.<sup>15</sup>

Our results show that male decedents did not experience dyspnea more frequently than female decedents, although Smith et al.<sup>4</sup> demonstrate

**Table 4 Odds ratio of symptom experience in female vs male elderly cancer decedents**

Symptom	Odds ratio unadjusted	95%CI	Odds ratio adjusted for age	95%CI	Odds ratio adjusted for age, ADLs, denentia, and cause of death	95%CI
Dyspnea	0.67	0.32– 1.39	0.68	0.32– 1.43	0.44	0.15– 1.29
Pain (uncontrolled)	1.47	0.61– 3.57	1.41	0.57– 3.47	2.32	0.65– 8.27
Pain (controlled)	0.68	0.33– 1.42	0.71	0.34– 1.49	0.48	0.18– 1.30
Coma	3.32*	1.55– 7.13	3.63*	1.65– 8.00	1.57	0.58– 4.24
Acute confusion	1.63	0.68– 3.91	1.84	0.75– 4.55	1.24	0.37– 4.10
Anxiety	0.66	0.21– 2.11	0.86	0.26– 2.86	1.01	0.19– 5.30
Dizziness	1.26	0.08–20.56	2.11	0.12–36.51	—	—
Nausea and Vomiting	2.10	0.93– 4.75	2.25	0.97– 5.19	3.95*	1.22–12.79
Anorexia	0.69	0.33– 1.46	0.67	0.31– 1.43	0.52	0.19– 1.49
Diarrhea	0.93	0.20– 4.37	0.78	0.16– 3.87	0.62	0.03–12.45
Constipation	1.62	0.41– 6.38	1.93	0.48– 7.77	1.46	0.25– 8.50
Fever	0.78	0.34– 1.82	0.78	0.33– 1.84	0.64	0.21– 1.97
Incontinence	1.28	0.47– 3.50	1.30	0.47– 3.61	0.55	0.16– 1.95
Hematemesis	0.41	0.04– 4.02	0.47	0.05– 4.72	—	—
Hemoptysis	—	—	—	—	—	—
Bottom blood	0.48	0.09– 2.58	0.46	0.08– 2.61	0.32	0.02– 4.65
Other hemorrhage	0.33	0.07– 1.67	0.34	0.07– 1.73	0.18	0.02– 1.99
Cough	0.81	0.27– 2.45	0.79	0.26– 2.43	1.00	0.22– 4.60
Sputum	0.38*	0.16– 0.89	0.38*	0.16– 0.90	0.24*	0.07– 0.81
Other symptom	0.85	0.36– 1.98	0.78	0.33– 1.86	0.74	0.24– 2.32

\*: significant differences were detected by uni- or multi-variable analysis

that dyspnea was worse in men than in women. Significant differences between the two groups may have been detected had this study investigated the severity of dyspnea.

Sputum experience was more common in male than in female decedents. Since sputum often leads to dyspnea, it might have been possible to relieve dyspnea symptoms in male decedents by treating for sputum. However, very little is known regarding sputum experience in the last days of life. Further studies are needed to shed light on this issue.

The present study demonstrates that nausea and vomiting experience was higher among female than male decedents. Although no significant differences were observed before adjustment, significant gender difference appeared after adjustment for age and other baseline characteristics. Thus, our findings are consistent with previous literature<sup>1,8,16-18</sup> in suggesting that female gender is an independent predictor of gastrointestinal symptoms such as nausea and vomiting.

Our data shows that there were no significant gender differences in pain experience. The fact that there was no significant gender difference in the use of opioids is strongly indicative of gender similarity in symptom experience. A number of studies have suggested that pain experience is more common in women than men. Because it is generally believed that pain is less common in elderly patients rather than younger cancer patients,<sup>8,19</sup> the absence of gender differences in pain experience in our study may have been due to the fact that our study sample was limited to elderly patients aged 65 and over. Also, it is difficult to interpret this finding, because in this study we did not assess the severity of pain. In future studies, a complete pain assessment should be included for a more comprehensive result.<sup>3</sup>

Also, in this population, acute confusion occurred equally in female and male decedents. According to Cobb et al.,<sup>2</sup> men are at higher risk of showing acute confusion. To our knowledge, no study has been conducted to investigate differences between female and male patients with

regard to the presence of acute confusion at end-of-life. Additional studies are needed to confirm gender differences in this respect.

Our study has a number of limitations. Because female decedents were significantly older than their male counterparts, it is likely that their disease was at a more advanced stage since disease progression is related to age. This may have had an impact on symptom experience in this group.

Also, the small number of patients and limited study settings may account for the lack of gender differences in symptom experience. In addition, the Japanese Society of Hospice and Home-care is interested in hospice and home-care, and selection bias is thereby also possible. Larger studies may reveal statistically significant differences between women and men in Japan.

Finally, our database does not systematically capture the full extent of the study subjects' characteristics that could affect symptom experience, especially the ability to convey symptoms.

## Conclusions

The purpose of this secondary analytic study was to evaluate the gender differences in symptom experience of elderly cancer patients at home during the last two days of life.

Patients' records indicate gender differences in the experience of symptoms such as nausea, vomiting, and sputum; in care receipt, however, no gender differences were noted. This study suggests that consideration should be given to gender differences in symptom experience and management at end-of-life. Additional studies should be conducted to supplement our knowledge on the subject and improve care.

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# Change of Plasma High Sensitive —C reactive protein levels in climbers

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Shintaro Suzuki,<sup>\*1–3</sup> Yuji Kiuchi,<sup>\*3,4</sup> Tetsuya Nemoto,<sup>\*3</sup> Kenta Kobayashi,<sup>\*3</sup> Hidekazu Ota<sup>\*2</sup>

## Abstract

**Rationale** Acute mountain sickness (AMS) is a high altitude illness. Previous studies report that levels of inflammatory indicators are higher at high altitudes. Therefore, inflammation is important for AMS.

**Objectives** We examined whether slight inflammation in mountain climbers could be detected with plasma levels of high sensitive C-reactive protein (hs-CRP). Next, we studied the relations of clinical parameters of plasma hs-CRP levels in AMS patients.

**Methods** (A) 32 healthy subjects were recruited to climb the mountain. We collected their blood in Tokyo (about 40 m above sea level) and in Mt. Kita Clinic (about 2,900 m above sea level). We measured plasma hs-CRP levels in their samples. (B) Next, we collected blood from 21 climbers diagnosed with AMS. We also measured hs-CRP levels in AMS patients and examined their relationship to clinical parameters of AMS.

**Results** Plasma hs-CRP levels of healthy subjects after climbing the mountain were significantly higher than before climbing ( $914 \pm 272$  ng/ml vs  $299 \pm 86$ ,  $P < 0.05$ ). Plasma levels of hs-CRP were much higher values in AMS patients ( $2,433 \pm 831$ ). They were correlated with AMS score ( $P < 0.001$ ,  $r = 0.658$ ), and symptomatic duration ( $P < 0.001$ ,  $r = 0.691$ ).

**Conclusion** These results showed slight inflammation existed in healthy climbers. Moreover, it was demonstrated plasma hs-CRP levels were related to clinical parameters of AMS. Therefore, hs-CRP was suggested to be an available and objective marker that could be used to evaluate the severity of AMS as an inflammatory disease.

**Keywords** Cytokine, High altitude medicine, High sensitive c-reactive protein, Mountain climbing, Stress failure

## Introduction

Trekking and mountain climbing are popular leisure activities with middle aged to elderly people in Japan, because of the recent fitness boom. However, many climbers have been injured or suffered illness when climbing. The most important matter for amateur climbers is to prevent high altitude illness, especially acute mountain sickness (AMS). AMS is characterized

by non-specific symptoms and a few physical findings. The main symptoms are headache, anorexia, nausea, vomiting, fatigue, dizziness and sleep disturbance, although all of them must not be present for diagnosis. These symptoms typically appear 6–12 hours after arrival at high altitude; over 2,500 m above sea level.<sup>1,2</sup> High altitude cerebral edema (HACE) and high altitude pulmonary edema (HAPE) are severe forms of AMS. The incidences of HACE and HAPE are much lower than AMS, but they are poten-

\*1 First Department of Internal Medicine, Showa University, School of Medicine, Tokyo; \*2 Second Department of Pathology, Showa University, School of Medicine, Tokyo; \*3 Mt. Kitadake Clinic, Showa University, School of Medicine, Yamanashi; \*4 Department of Pathophysiology, Showa University, School of Pharmaceutical Sciences, Tokyo

Correspondence to: Shintaro Suzuki MD, First Department of Internal Medicine, Showa University, School of Medicine, 1-5-8 Hatanodai, Shinagawa-Ku, Tokyo 142-8555, Japan. Tel: 81-3-3784-8532, Fax: 81-3-3784-8742, E-mail: szshin@yahoo.co.jp

**Table 1 Characteristics of healthy subjects**

Number of subjects	32
Age (years old)	23.1 ± 2.4
Gender (M:F)	20:12
Past history	bronchial asthma in 2 subjects (remission) allergic rhinitis in 5 subjects (remission) Kawasaki disease in 1 subject (remission)

tially fatal.<sup>3,4</sup> Since there are no high mountains over 4,000 m in Japan, the high altitude illness that occurs is AMS in most cases.

Past studies show that hypobarism, hypoxia and excessive exercise may cause AMS.<sup>3,5,6</sup> However, the pathophysiology of AMS has not been fully clarified. Its fundamental pathophysiology is supposed to be disorder in the capillary vascular wall. Oxidative changes and subsequent inflammatory response are thought to be involved in its progress.<sup>1,7,8</sup> Previous studies evaluated AMS as an inflammatory disease by observation of the blood levels of several inflammatory markers such as inflammatory cytokines, chemokines, white blood cells count and C-reactive protein (CRP).<sup>9</sup> However, no researchers have evaluated the plasma CRP levels in AMS patients with high-sensitive assays, but with only conventional assays. With high-sensitive CRP (hs-CRP) assays, we can detect inflammatory changes in earlier phases of diseases than usual assays, so that hs-CRP assays are not being used to evaluate the prognosis of lifestyle diseases in clinical metabolic medicine.

Mild to moderate grade AMS can usually be resolved by descending the mountain. Therefore, studies on mild to moderate grade AMS have not progressed. Furthermore, as previous studies on AMS were usually performed with a passive ascent to high altitude or by simulation tests in a hypobaric chamber, they might not necessarily reflect the current state of AMS patients. In particular, the relation between mild to moderate grade AMS and inflammation in the early phase of AMS is unknown.

In this study, we examined whether the plasma levels of hs-CRP were a possible marker of the early phase of AMS in two independent studies. First, we evaluated the change of plasma levels of hs-CRP in healthy climbers between before and just after climbing a mountain. Next, we

examined the plasma levels of hs-CRP in AMS patients who consulted our mountain clinic and evaluated the relation between plasma levels of hs-CRP and known clinical parameters in AMS.

## Material and methods

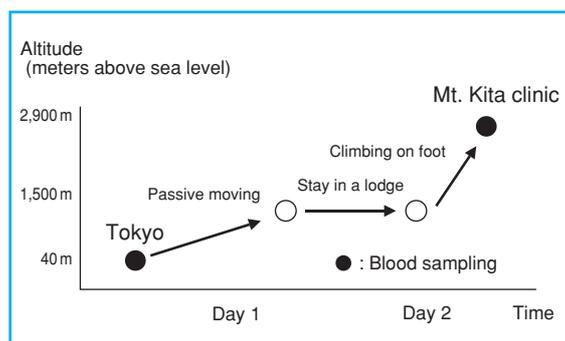
### Participants and subjects

Mt. Kita is the second highest mountain in Japan (3,192 m above sea level, in Yamanashi Prefecture). In 1985, Showa University School of Medicine established the clinic on Mt. Kita (about 2,900 m) for climbers suffering from diseases and injuries, and it is open every summer from July to August. Each summer, about 250–300 climbers visit the clinic, and two-thirds of them are AMS patients.

We examined two independent studies as follows (A and B).

Study (A): We recruited 40 healthy subjects to climb the mountain. Of these, 2 subjects withdrew, and as 6 persons had several symptoms that could possibly be caused by a high altitudinal environment, they were excluded from the study. So, a total of 32 subjects climbed the mountain route to Mt. Kita Clinic in safety. They did not complain of AMS symptoms and did not have any abnormal findings. They consisted of 20 men and 12 women ranging in age from 20 to 26 years old (Table 1). All subjects resided at altitudes <100 m above sea level. As for past history, 2 persons had remittal bronchial asthma, and 5 persons had allergic rhinitis. One subject had a past history of Kawasaki disease, but it was in remission. One person was a current smoker.

The plan of the climb is shown in Fig. 1A. On the first day, they arrived at the foot of Mt. Kita (1,529 m) from Tokyo by train and bus. They stayed overnight in a lodge and started climbing from 6:00 the next morning. Everyone climbed to the clinic via the same climbing route decided



**Fig. 1A**

Hirogawara in Minami-Alps city, Yamanashi Prefecture, is an entrance for Mt. Kita. The average course takes about 6 to 10 hours for adults.

**Table 2 Characteristics of AMS patients**

Number of patients	21
Age (years old)	52.2 ± 1.8
Gender (M:F)	8:13
AMS score (points/full 23)	6.3 ± 0.2
Duration (hours)	6.4 ± 0.9
Climbing altitude (maximum; m/day)	1,043 ± 115.6
Climbing courseroute	A*1:B*2 = 14:7
hs-CRP (ng/ml)	2,433 ± 831
TC (mg/dl)	194.9 ± 9.7
TG (mg/dl)	81.1 ± 10.3
BMI (kg/m <sup>2</sup> )	21.8 ± 2.6

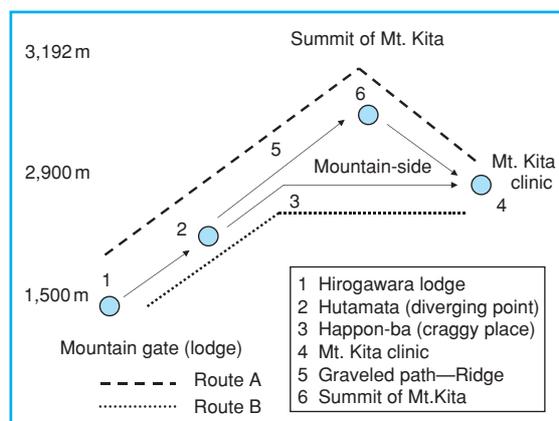
Data was shown as mean ± S.E.M. except number patients, gender and climbing courseroute.

\*1: Via the peak of Mt. Kita (3,192 m)

\*2: Not through the peak

by us. Although they did not pass through the peak of Mt. Kita, it took from 7 to 9 hours. They ascended about 1,371 m per day. The altitude from Tokyo was about 2,860 m. It was good weather throughout the program. The weight of each person's luggage was less than 10 kg.

They were permitted to take food and drink from Tokyo to the clinic. However, they were instructed to avoid certain foods, supplements, and medicine such as vitamins reported to have anti-oxidative effects, for at least 1 week before the collection of blood in Tokyo. We allowed them to take medicine for therapy. There were no restrictions on the times of urination and



**Fig. 1B**

The most popular course is Route A (1→2→3→4), and the second most popular is Route B (1→2→5→6→4). Neither route was snow capped. Subjects selected various routes.

defecation. No one inhaled oxygen during or after climbing.

Study (B): Twenty-one AMS patients participated in our second study. They climbed the mountain on foot and consulted our clinic when they complained of symptoms. Each climber gave his or her informed consent. They consisted of 8 men and 13 women, ranging in age from 34 to 66 years with an average age of 52.2 ± 1.8 years old (Table 2). Physicians performed clinical examinations on them and diagnosed them with AMS. Collection of blood samples was performed in the clinic. As patients climbed in various parties, their climbing routes differed. We divided them into two groups according to whether or not they reached the peak of Mt. Kita (3,192 m) (Fig. 1B). Fourteen patients via route A reached the peak. Fifteen patients had recurrent episodes of high altitude illness. Five patients had a past history, such as myoma uterus, gout, allergic dermatitis, allergic conjunctivitis and chronic sinusitis. Two persons were current smokers. No patients smoked or drunk alcohol while climbing the mountain.

The study was approved by the ethics committee of Showa University School of Medicine and informed consent was obtained from all subjects.

#### Collection, separation and store of blood sample

Blood samples (9 ml) were drawn from the

antecubital vein. All the blood samples were taken using sterilized plastic syringes, and placed in plastic tubes including EDTA. Within 10 min, plasma and serum were separated from each sample by centrifugation and immediately frozen at  $-30^{\circ}\text{C}$  until measurement. Frozen samples were transported to a laboratory in Showa University in a cooler to avoid defrosting.

Subjects of Study (A): Baseline blood sampling was performed 2–3 weeks before climbing in Tokyo (about 40 m). Blood was drawn from 14:00–16:00, before dinner. This timing was matched to the arrival time at the clinic. In the mountain, drawing of blood was performed within 1 hour after they arrived at Mt. Kita Clinic.

Subject of Study (B): Blood was drawn from AMS patients after medical examination in the clinic.

#### Measurement of plasma levels of hs-CRP

We requested SRL Co. (Tokyo, Japan) to measure hs-CRP in 500  $\mu\text{l}$  plasma samples. It was performed according to the method of latex agglutination assay with Behring Nephelometer and N Latex CRP (Dade Behring). The lower limit of this test was 50 ng/ml (0.05 mg/dl). When measured values were above the limits, they were expressed as the actual values.

The assays for CRP are mainly used for detecting infection and inflammatory diseases. The upper reference value of the conventional CRP assay is mostly 0.2 to 0.5 mg/dl. The precision of the assay with the low-normal range is not satisfactory. High sensitivity assay for CRP has recently become commercially available and is used for predicting cardiovascular disease and managing metabolic syndrome.<sup>10</sup> This assay is 40 times as sensitive as usual assays. The normal range of hs-CRP in Japanese is thought to be from 1,000 to 10,000 ng/ml (from 0.1 to 1 mg/dl). In some clinical cases, plasma levels of hs-CRP have been reported to be useful for the diagnosis of inflammatory disease such as infection or acute coronary syndrome in the super-early phase.<sup>11–13</sup>

#### Calculating of body mass index (BMI)

As hs-CRP is affected by obesity and hyperlipemia,<sup>10,14,15</sup> we also evaluated body mass index, total serum cholesterol levels and triglycerides levels in all subjects.

BMI as an indicator of obesity was calculated

with height and body weight. BMI was expressed as body weight [kg]/(height [m])<sup>2</sup>. Obesity was defined as over 25 kg/m<sup>2</sup>.

#### Measurement of total serum levels of cholesterol (TC) and triglyceride (TG)

Serum levels of total cholesterol and triglyceride were measured using E-test WAKO (WAKO, Japan) and spectrophotometer (HITACHI, Japan).

#### Measurement of serum levels of interleukin-8 (IL-8), interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF)

For only subjects of Study (A), serum levels of IL-8 and VEGF were measured by the methods of enzyme linked immunosorbent assay (ELISA) using Quantikine (R&D, Minneapolis, USA) ELISA kit. Serum levels of IL-6 were measured by the methods of high sensitivity ELISA using the same kit. The reference values of IL-8, IL-6, and VEGF were respectively 8.0 pg/ml, 2.41 pg/ml, and 38.3 pg/ml.

#### Evaluation of the Lake Louise score (AMS score)

All patients who consulted our clinic were scored for AMS according to the interview form called the Lake Louise Consensus scoring system (Lake Louise Consensus Questionnaire (LLCQ))<sup>16,17</sup> translated into Japanese. This questionnaire comprised 8 items to ask climbers the degree of AMS symptoms such as headache, gastrointestinal symptoms, fatigue, dizziness and insomnia etc. Each item is scored with 0, 1, 2 or 3 points. The presence of AMS was defined as a cumulative score  $\geq 5$  points out of 23 for the total Lake Louise score. The system is usually called AMS scoring. We used the AMS score for evaluating the severity grade of AMS.

#### Noninvasive measurement of arterial oxygen saturation (SaO<sub>2</sub>)

For subjects of Study (B), SaO<sub>2</sub> was measured noninvasively with a pulse oxymeter finger probe (PULSOX 7, Minolta, Japan), three times for each patient, and the mean values were recorded.

#### Statistical analyses

STAT view Ver5.0 (SAS Institute; Cary, NC) was used for the statistical analysis. Paired *t*-test was used for comparison of the plasma levels of hs-CRP and the serum levels of IL-6, IL-8

**Table 3 Plasma levels of inflammatory indicators of healthy subjects**

(ng/ml)	Before	After	<i>P</i>
hs-CRP	914 ± 272	299 ± 86	<0.05
(pg/ml)	Before	After	<i>P</i>
IL-6	1.21 ± 0.25	0.88 ± 0.40	NS
IL-8	16.0 ± 9.5	10.5 ± 2.67	NS
VEGF	300.2 ± 3.27	296.1 ± 52.67	NS

Mean ± S.E.M.

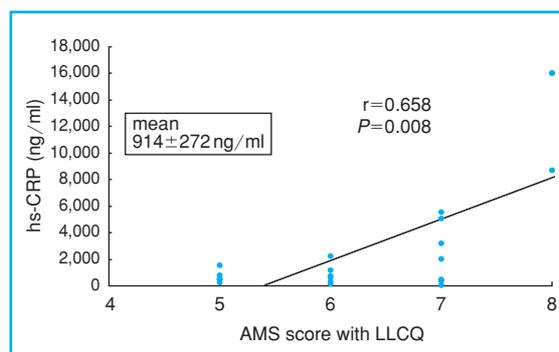
and VEGF between before and after climbing. Pearson's correlation coefficient was used between the plasma levels of hs-CRP and other AMS parameters. All values are shown as mean ± SEM. A *P* value <0.05 was considered statistically significant.

## Results

### Study (A) with healthy subjects

Plasma levels of hs-CRP in healthy subjects after climbing were significantly higher than those before climbing (914 ± 272 ng/ml vs 299 ± 86, *P*<0.05) (Table 3). Serum total cholesterol and triglyceride levels were within normal limits (TC 146.7 ± 6.0 mg/dl, TG 93.77 ± 11.87 mg/dl), and did not correlate with their plasma levels of hs-CRP. The mean value of BMI was 20.7 ± 1.4 kg/[m]<sup>2</sup>, and did not correlate with hs-CRP. Furthermore, there was no correlation with age or gender. All participants were checked by a physician and no infectious symptoms were found.

In levels of IL-6, IL-8 and VEGF in the serum of healthy climbers, no significant difference was seen between after and before climbing. However, the serum levels of IL-8 tended to be higher after climbing than those before climbing (16.0 ± 9.5 pg/ml vs 10.5 ± 2.7 pg/ml, NS). Serum levels of IL-6 also tended to be higher after climbing than those before climbing (1.21 ± 0.25 pg/ml vs 0.88 ± 0.40 pg/ml, NS). Serum levels of VEGF showed no difference between before and after climbing (300.2 ± 32.7 pg/ml vs 296.1 ± 52.7 pg/ml, NS). There was no correlation between plasma hs-CRP levels with either of the above serum cytokines levels.

**Fig. 2**

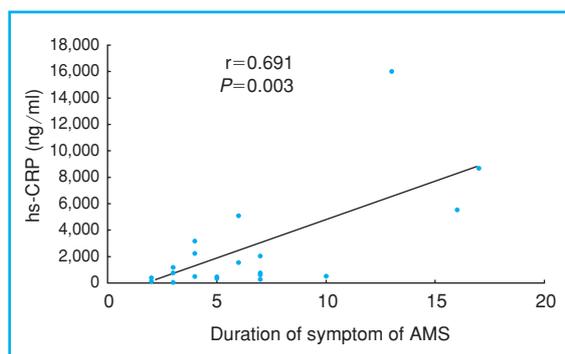
Average AMS score of patients was 6.3 ± 0.2. The highest AMS score in the patients was 8. Plasma levels of hs-CRP in AMS patients significantly correlated with their AMS scores.

### Study (B) with AMS patients

The plasma levels of hs-CRP in AMS were significantly higher than those in healthy climbers after climbing (2,433 ± 831 ng/ml vs 914 ± 272 ng/ml, *P*<0.05). Most AMS patients did not have lifestyle diseases, but 1 person was being treated for gout. Total amounts of cholesterol and triglyceride of the patients were TC 194.9 ± 9.7 mg/dl, TG 81.1 ± 10.3 mg/dl, respectively. Calculated BMI was 21.8 ± 2.6 kg/m<sup>2</sup> in AMS patients (Table 2). Four patients showed abnormal data on lipid metabolism and 1 patient was obese, but their plasma hs-CRP levels did not correlate with blood lipid levels.

AMS was diagnosed by physical examinations and AMS score with LLCQ. In this study, we diagnosed AMS when the AMS score was higher than 5. The average AMS score of patients was 6.3 ± 0.2. The highest AMS score in patients was 8. Therefore, the severities of AMS in this study were mostly mild to moderate. Plasma levels of hs-CRP in AMS patients significantly correlated with their AMS scores (*P*=0.008, *r*=0.658) (Fig. 2).

Some climbers complained of symptoms while climbing and other climbers developed AMS after climbing. The duration from onset of symptomatic AMS varied. The average duration calculated with clinical records, was 6.4 ± 0.8 hours. Plasma levels of hs-CRP in AMS patients significantly correlated with the duration of AMS (*P*=0.003, *r*=0.691) (Fig. 3). Plasma levels



**Fig. 3**

Duration from the onset of symptomatic AMS varied. The average duration calculated from clinical records, was  $6.4 \pm 0.8$  hours. Plasma levels of hs-CRP in AMS patients significantly correlated with the duration of AMS.

of hs-CRP did not correlate with age, gender, body temperature,  $\text{SaO}_2$  or other clinical parameters.

## Discussion

Mountain climbing increases serum levels of inflammatory mediators such as cytokines and chemokines in mountain climbers. For example, IL-1 $\beta$ , IL-6, IL-8, tumor necrotizing factor- $\alpha$  and CRP have been reported to be increased in peripheral blood and related to high altitude diseases.<sup>5,9,18-21</sup> Previous studies with conventional assays showed plasma levels of CRP elevated some days after climbing or passive movement to highlands.<sup>9,18,19</sup> However, these studies did not show slight inflammation caused by climbing in the early term. In this study, we studied the plasma levels of hs-CRP in mountain climbers including AMS patients just after climbing. Our results show that the plasma levels of hs-CRP in healthy subjects after climbing are significantly higher than those before climbing. These findings indicate the possibility of slight inflammation in healthy subjects in the early term after climbing.

Our results also suggest that plasma hs-CRP levels are more sensitive to evaluating slight inflammation caused right after climbing than serum IL-6, IL-8, or VEGF levels. Previous studies reported that the increase of plasma levels of IL-6 and VEGF after exposure to high altitude were greater than the other proinflammatory cytokines.<sup>19-21</sup> However, in this study,

inflammatory cytokines or chemokines levels might be too small to evaluate in the early phase, in healthy climbers without complaint. Inflammatory mediators are likely to be less activated in high altitudinal illness than systemic inflammatory disease, since they are reported to be usually around normal limits.<sup>9</sup>

Furthermore, we examined plasma hs-CRP levels in mild to moderate grade AMS patients who had climbed the mountain on foot. In past studies, most subjects were patients with severe AMS or HAPE who were carried to a hospital at low altitude, where they were examined and treated. In contrast, blood was drawn just after diagnosis of mild to moderate grade AMS in this study, and our results reflected the current status of the patients. Plasma hs-CRP levels in AMS patients were found to be much higher than those in healthy subjects after climbing, although precise comparison is difficult because of differences in biological background (e.g. age or gender) between healthy subjects and patients. Therefore, we supposed that measurement of CRP was suitable for detection and diagnosis of AMS in the early term. We speculated that production of CRP began immediately after exposure to a high altitudinal environment and that AMS aggravated inflammation in climbers and promoted CRP production, while there was a possibility that plasma hs-CRP was increased partly due to excessive exercise during climbing. Also, the plasma levels of CRP in AMS patients were significantly correlated with AMS score and the symptomatic duration of AMS, suggesting possible correlation between the plasma levels of CRP and the severity of AMS. Therefore, hs-CRP may be an objective marker for evaluating the severity of AMS.

The etiology of AMS has been not been clarified. Complementary hypoventilation, impaired gas exchange, fluid retention and redistribution are thought to be involved.<sup>22</sup> Also, the elevation of intracranial pressure is often observed in cases of severe AMS and HACE. However, patients even in these cases felt better by descending, and usually did not see the doctor after convalescence, so little clinical data has been accumulated. However, some pathophysiological features of HAPE, the severity type of AMS, have been speculated from the data of inpatients suffering from HAPE as follows. Human vessels were injured by rapid exposure to a high alti-

tudinal environment such as hypobarism and hypoxia, and by endurance exercise, resulting in endothelial injury and capillary leakage, so-called “stress failure.” Edema, inflammation and oxidative change were consequently raised in various organs.<sup>1,2,7,22–24</sup> Those events that occurred in the gastro-intestine, lung and brain were considered to lead to AMS symptoms. Acetazolamide as a diuretic was thought to be effective for edema of AMS. However, at pres-

ent, there is no specific remedy for AMS without symptomatic treatment and rapidly descending. Further studies on the pathophysiology of high altitude illness are required to improve the safety of mountain climbing.

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# The Effectiveness of a New Law to Reduce Alcohol-impaired Driving in Japan

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Takashi Nagata,<sup>\*1–3</sup> David Hemenway,<sup>\*4</sup> Melissa J Perry<sup>\*5</sup>

## Abstract

**Objectives** To estimate the impact of a new traffic law targeting alcohol-impaired driving in Japan

**Methods** Japan passed a new traffic law in June 2002 with the aim of reducing the incidence of alcohol-impaired driving by reducing the permissible blood alcohol level and increasing penalties. Using data collected from police reports, the number of traffic fatalities and injuries for 7 months in the pre-law period (June 2001 to December 2001) and the same 7 months in the post-law period (June 2002 to December 2002) were compared.

**Results** Traffic fatalities decreased 7.8% and traffic fatalities involving alcohol-impaired driving decreased 26.7% after the introduction of the new traffic law. Traffic fatalities had been falling since 1993, but fell substantially faster after the law was passed.

**Conclusions** This study indicates that large, immediate public health benefits resulted from the implementation of the 2002 alcohol-impaired driving law in Japan.

**Key words** Alcohol, Driving, Traffic, Breath test

## Introduction

Traffic injuries are a world-wide public health issue. Annually, more than a million people are killed on the world's roads; in the United States alone, there are over 40,000 motor vehicle fatalities each year.<sup>1</sup> In April 2004, The World Health Organization (WHO) and The World Bank released the *World Report on Road Traffic Injury Prevention*.<sup>2</sup> The report stated that in 1990, road traffic injuries were the ninth largest contributor to the global burden of disease, but are predicted to become the third largest contributor by 2020 unless appropriate action is taken.

Alcohol-impaired driving is a leading cause of traffic fatalities both in developed and developing countries. A review of studies in low- and middle-income countries found that blood alco-

hol was detected in 33–66% of fatally injured drivers. Although drinking and driving legislation, including administrative measures, random screening, and lowering of the legal blood alcohol limit, has been shown to reduce traffic fatalities, many countries have not implemented such measures.<sup>3</sup>

In Japan, traffic accident fatality rates have been decreasing 3–4% per year since 1992. The absolute number of traffic deaths has also fallen, from 11,451 in 1992 to 8,877 in 2003. The National Police Department believes that this reduction is due to improvements in policy, roads, vehicle engineering, driver behavior, and the nation's emergency medical system.<sup>4</sup>

In the 1990s, blood alcohol was detected in 14–16% of fatally injured drivers in Japan.<sup>5</sup> In order to reduce alcohol-related traffic fatalities, in June 2002, the Japanese Government enacted

\*1 Takemi Program, Department of International Health, Harvard School of Public Health, Boston, USA; \*2 Department of Emergency Medicine, Saint Mary's Hospital, Kurume; \*3 Japan Medical Association Research Institute, Tokyo; \*4 Department of Health Policy and Management, Harvard School of Public Health, Boston, USA; \*5 Department of Environmental Health, Harvard School of Public Health, Boston, USA  
Correspondence to: Takashi Nagata MD, Emergency Department, Saint Mary's Hospital, 422 Tsubukuhonmachi, Kurume, Fukuoka 830-8543, Japan. Tel: 81-942-35-3322, Fax: 81-942-34-3115, E-mail: nagata.takashi@gmail.com

**Table 1 Incidence of motor vehicle injuries in Japan (2003)**

	Total No.	per population (per 100,000)
Total population	127,435,000	
Fatalities (death within 30 days)	8,877	7.0
Severe injuries <sup>a</sup>	75,086	58.9
All injuries	1,181,431	927
Injury fatality rate	0.75%	

<sup>a</sup>: injuries that resulted in more than 30 days of medical care

a new Road Traffic Law targeting alcohol-impaired driving. This law lowered the breath alcohol reading allowed when driving from 0.25 to 0.15 mg/L (equal to 0.03% blood alcohol concentration), and increased the penalties for alcohol-impaired driving. The fine increased from approximately 50,000 to 500,000 yen (425 to 4,250 USD) and severe driver's license point deductions were imposed.<sup>5</sup>

This study evaluated the impact of this new law on traffic fatalities in Japan. We compared the occurrence of traffic fatalities between the same 7 month periods before and immediately after the new law was implemented.

## Methods

This study utilized data available in the public domain, and received human subjects exemption from the Harvard School of Public Health IRB committee.

Simple counts were made of nationwide traffic fatalities from June to December 2001 (pre-law) and June to December 2002 (post-law), the first seven months after the new law was enacted, and the data for the two periods compared. Data came from police traffic accident reports. In Japan, regional police agencies report to a central national police agency. The national agency had a clear protocol for how the data were to be collected which included using information supplied by emergency medical care professionals.

A traffic fatality was defined as a person who dies within 24 hours of an accident on a road involving a vehicle with an engine, the death being the result of the accident. Thus fatality data included all motor vehicle-related deaths (involving, for example, trucks, motorcars, motor-

cycles, bicycles, and/or pedestrians). The total number of traffic fatalities, alcohol-related fatalities, injuries (non-fatal and fatal), and alcohol-related traffic arrests were compared between the two periods. In Japan, it is illegal to drive a car under the influence of alcohol. Alcohol-impaired driving (AID) is defined as driving with an alcohol reading >0.15 mg/L measured in a breath test.

Data-analysis was performed using STATA ver.8. Chi-square tests were used to compare fatality rates between the two periods.

## Results

In Japan in 2003, there were 8,877 traffic fatalities within 30 days of traffic accidents, 7.0 per 100,000 persons (Table 1). Traffic injuries totaled 1,181,431, or 927 per 100,000 persons. Severe injuries, defined as casualties who received medical care for more than 30 days, totaled 75,086, or 58.9 per 100,000 persons. The ratio of traffic fatalities to severe traffic injuries to total traffic injuries was 1:8.4:132.

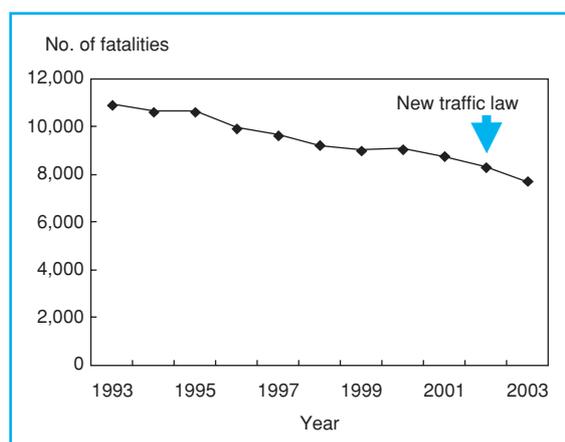
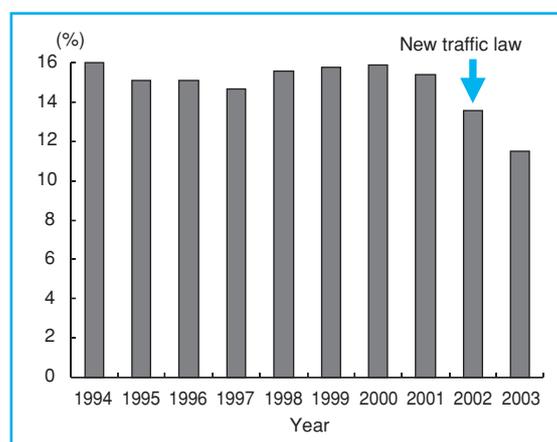
Total traffic fatalities decreased 7.8% after the introduction of the new traffic law ( $P<0.05$ ) (Table 2). Traffic fatalities associated with alcohol-impaired driving decreased by 26.7% ( $P<0.0001$ ). Although the legal drinking threshold was lowered by the new law, the number of drivers arrested for alcohol-impaired driving fell 4.6%.

Traffic fatalities have been decreasing in Japan since 1993 (Fig. 1). In the one year that fatalities did not decrease, 1995, Japan experienced the Great Hanshin Earthquake, and diagnosis coding changed from ICD-9 (International Classification of Diseases, 9th revision) to ICD-10. The average percentage fatality rate decrease between

**Table 2** Number of traffic injuries and fatalities in Japan pre- and post-law (June–December 2001 compared to June–December 2002)

	Pre-law	Post-law	Percentage change	
No. of injuries	553,236	535,392	-3.2%	*
No. of injuries related to alcohol-impaired driving	14,861	10,853	-27.0%	
No. of fatalities	4,778	4,403	-7.8%	*, **
No. of fatalities related to alcohol-impaired driving	712	522	-26.7%	**
Total no. of regulated vehicles	6,776,773	6,601,364	-2.6%	
No. of drivers arrested for alcohol-impaired driving	140,460	133,937	-4.6%	

Statistically significant (\*:  $P < 0.05$ , \*\*:  $P < 0.0001$ ), using Chi-square test

**Fig. 1** Occurrence of traffic fatalities since 1993**Fig. 2** The percentage of total fatalities resulting from AID

1993 and 2002 was 2.9% per year. Assuming that this decrease rate was stable on average, we applied it to the results in Table 2. Using this method, we estimated that  $4,778(1-0.029) = 4,639$  people would have died in the 7-month post-law period. However, the actual number of traffic fatalities was 4,403, a difference of 236 people ( $4,639 - 4,403$ ).

From 1993 to 2001, the percentage of total fatalities that were related to alcohol-impaired driving was 15.5%; this number fell to 13.6% in 2002, and to 11.5% in 2003 (Fig. 2).

## Discussion

Following implementation of the 2002 Road

Traffic Law, which increased the penalties for alcohol-impaired driving, Japan experienced a substantial drop in alcohol-related driving fatalities (26.7%) and a fall in total traffic fatalities. While traffic fatalities in Japan had been decreasing since the early 1990s, it appears that the law accelerated that trend. Shimizu and Imai reported the decrease in traffic fatalities after the new law, but did not measure the effect against the already declining traffic fatalities in Japan since 1993.<sup>5,10</sup>

Alcohol remains a major contributor to traffic death throughout the world, although much progress has been made. License suspension, illegal and administrative per se laws, selective and regular enforcement patrols, and sobriety check-

points have been effective in reducing the harm caused by alcohol-impaired driving.<sup>6,7</sup> The introduction of a legal blood alcohol concentration (BAC) limit has been effective in the United Kingdom, Canada, the Netherlands, and Japan. A 1970 law in Japan, which set the legal BAC at 0.05%, seems to have reduced traffic fatalities, but it was not statistically evaluated.<sup>7,8</sup>

The 2002 law had two major features. First, it set the legal limit for a breath alcohol test reading at 0.15 mg/L, and that for a BAC at 0.03%/mg.

In Japan, breath testing is usually used to measure BAC because it is easy for police to perform.

The second major feature of the law was an increase in the penalty for drunk-driving from 425 to 4,250 USD (50,000 to 500,000 yen), an amount of money higher than the average monthly salary of businessmen who have graduated from university. Moreover, the new law placed responsibility not only on the alcohol-impaired driver but also bartenders who encouraged drinking and passengers who failed to discourage impaired driving.

Japan publicized the new law in a variety of ways, including mass media campaigns. However, the police stated that they did not change their alcohol related activities after June 2002, and the total number of arrests before and after the law was implemented was similar (Table 2). Stronger police enforcement does not appear to have been the cause of the drop in alcohol-related fatalities.

We measured the impact of the new law on the decrease in traffic fatalities in two ways: 1) by assuming that the number of injuries would have otherwise remained the same without the law, and then 2) by assuming that the rate of decrease in the number of injuries from 1993–2001 would have continued through 2002 and 2003. Both approaches showed the impact of the

law to have been significant.

This study has various limitations. First, data were not available on the severity of the non-fatal injuries in general, or on the severity of non-fatal alcohol-related injuries in particular. Second, we used the number of deaths within 24 hours of the traffic accident, not the number within 30 days. In most developed countries, traffic fatalities within 30 days of an accident are the standard measurement. Third, we did not control for possible confounders. However, we do not know of any other changes or events that occurred between 2001 and 2003 that may have had a significant impact on traffic injuries.

Our study reinforces and expands on previous reports that presented early results concerning the law.<sup>9,10</sup> By all appearances, the law was quite successful. The number of alcohol-related motor vehicle fatalities and injuries fell by over 25%. The percentage of fatalities involving alcohol also fell substantially. However, even before the law, drunk-driving was less of a problem in Japan than in many other countries, representing less than 16% of total traffic fatalities. In the United States, this figure is about 40%. Part of the difference may be due to life style factors; in urban Japan parties are often held in bars, but patrons go home by public transport. The existence and use of an efficient and safe public transportation system may be a prime explanation for the lower rates of drunk-driving problems in Japan, particularly in urban areas.<sup>9</sup>

Our study found that the new Road Traffic Law was immediately followed by a substantial decline in fatal and non-fatal motor vehicle injuries associated with alcohol-impaired drivers, and an overall decrease in motor vehicle deaths and injuries. This Japanese policy appears to have been a very successful public health measure.

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# Child Abuse in Japan: Current problems and future perspectives

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Makiko Okuyama\*<sup>1</sup>

## Abstract

Over the past 15 years, significant progress has been achieved in the intervention of child abuse. However, while the number of child abuse cases discovered has increased, there has been no decrease in the number of cases of children dying as a result of abuse. The role healthcare has to play in saving such children is increasingly important, but at present we cannot really say that a healthcare system for treating abuse has been established. This paper examines the current situation of medical system regarding child abuse treatment in Japan, presenting an overview of the issues now requiring attention, particularly the need for: 1) education of child abuse for all physicians and other healthcare personnel; 2) establishment of internal hospital systems for child abuse; 3) establishment of community healthcare systems for intervention of child abuse; 4) collaboration between various medical fields for child abuse; 5) establishment of abuse treatment as a specialized medical field; and 6) establishment of child death review system.

**Key words** Child abuse in Japan, Japanese child abuse prevention system, Child abuse law, Medical problems of child abuse

## Number and Characteristics of Reported Child Abuse Cases

Figure 1 shows changes in the number of child abuse cases reported to child counseling centers in Japan. In the United States, the number of reported child abuse cases is decreasing,<sup>1</sup> but the number in Japan continues to increase at a rapid pace. A particular characteristic of child abuse in Japan is the extremely low proportion of sexual abuse cases reported.<sup>2</sup> Figures for not only the United States and other countries at the forefront of child abuse treatment but also for Asian countries show physical and sexual child abuse to be equally high, followed by psychological abuse, or neglect.<sup>3</sup> In Japan, however, the proportion of sexual abuse cases is very low at approximately 3%. The proportion of cases reported by medical institutions is also very low (approximately 4%),

another characteristic of child abuse in Japan. However, these characteristics do not necessarily indicate the nature of child abuse in Japan so much as the problem of low social awareness of the need to protect children when sexual abuse is discovered. Nonetheless, clinically there has been an increase in recognition of sexual abuse; the number of sexual abuse cases reported in Japan is therefore expected to rise sharply in the future.

## The History of Countermeasures against Child Abuse in Japan

Specialists conscious of child abuse began researching and educating about the issue in the late 1970s, but in Japan it was not until the 1990s that the term *gyakutai* (“abuse”) gained popular recognition and treatment of child abuse began to move forward. From 1991, the recognition

\*1 Department of Psychosocial Medicine, National Center for Child Health and Development, Tokyo  
Correspondence to: Makiko Okuyama MD, Department of Psychosocial Medicine, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan. Tel: 81-3-3416-0181, Fax: 81-3-3416-2222, E-mail: okuyama-m@ncchd.go.jp

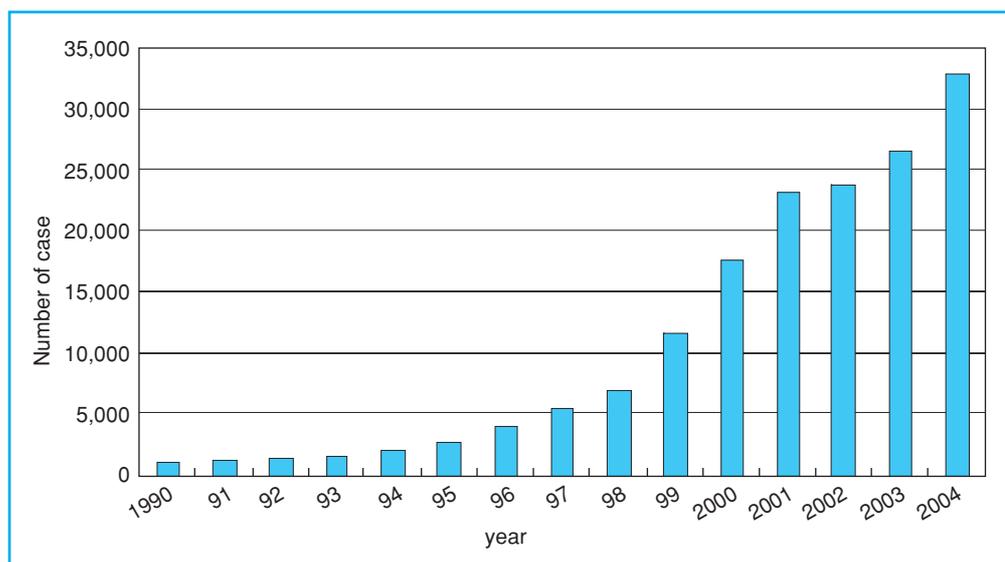


Fig. 1 Number of reported child abuse cases

and treatment of child abuse was led by NGOs established throughout the country, starting with bases in Tokyo and Osaka. These NGOs made possible multidisciplinary measures, introducing an intervention model that had until then been difficult to implement with the government's vertical administrative structure. Furthermore, in addition to collaborating with the mass media to spread awareness of child abuse among the general public, the NGOs have pursued methods for recognizing abuse situations and providing support through telephone counseling and other means.<sup>4</sup>

During the early 1990s, the Japanese government had taken a skeptical attitude towards the existence of child abuse, but in fiscal 1996 began to implement models and programs seeking collaboration with NGOs and proactively promote measures to prevent child abuse. Memoranda regarding the interpretation and application of the Child Welfare Law in recognizing and treating child abuse were issued in succession and child counseling centers were directed to proactively intervene rather than take the passive wait-and-see approach previously advocated. Moreover, from 1999 surveys detailing the number of abuse cases resulting in death despite the involvement of child counseling centers aroused social concern for this problem.

These large popular movements prompted

lawmakers to enact and enforce child abuse legislation, in the form of the Child Abuse Prevention Law, in 2000. Although the initial legislation was no more than a compilation of previous Child Welfare Law and Ministry of Health and Welfare (now the Ministry of Health, Labour and Welfare) memoranda, laws specific to child abuse were established. By clearly stipulating that child abuse exerts a profound effect on the remainder of abused children's lives, providing clear definitions, and imposing a responsibility on doctors and specialists to endeavor to identify child abuse cases early, this legislation represented tremendous progress. The new legislation also made reporting child abuse cases easier for medical professionals by stipulating that the reporting of such cases did not violate confidentiality under the Medical Practitioners Law.

## New Directions in Child Abuse Intervention

### Directions in social awareness

Establishment of the Child Abuse Prevention Law in 2000 resulted in a leap in the already-increasing number of child abuse cases reported to child counseling centers (Fig. 1). The Child Abuse Prevention Law contained a provision under which the law was to be reviewed in three years; after extensive debate on all quarters,

the law was amended in March 2004. The Child Welfare Law was amended at the same time, demonstrating a new direction in the recognition and intervention of child abuse. Article 1 of the Amended Child Abuse Prevention Law stipulates that “Child abuse seriously infringes upon the human rights of children,” an addition concerning human rights that was left out of the initial Child Abuse Prevention Law due to strong opposition from the ruling LDP party. With regard to reporting child abuse, “those discovering children that are being abused” was amended to “those discovering children that are believed to be being abused,” prescribing a clear responsibility to report any suspicion of child abuse. Other amendments include: the addition of “witnessing domestic violence (DV)” to the definition of child abuse; clear stipulation of the responsibilities of national and local government bodies; addition of not only individual specialists but of specialist organizations to those with a responsibility to endeavor to identify child abuse cases early; prescription of cooperation by those individuals and organizations responsible for identifying child abuse in the protection of abused children and with national and local government bodies in the formulation of policies; and prescription of consideration of the possibility of abuse of children entering nursery school or kindergarten and other educational issues concerning abused children. In other words, both doctors and medical institutions now bear a responsibility to not only identify child abuse cases early, but also cooperate in the protection of children and other relevant policies.

However, the greatest change regarding the recognition and treatment of child abuse was the regional focus established by the amendment of the Child Welfare Law. Children who have been abused or otherwise need society’s protection are deemed “Children Requiring Care”; municipalities are able to establish either independently or jointly in collaboration with relevant organizations regional councils for implementing measures to assist Children Requiring Care (hereunder referred to as “councils”); and municipalities receiving reports of child abuse ensure the safety of “Children Requiring Care” while at the same time provide support for the child and the child’s family. However, cases where specialist intervention is thought to be required must be referred to a child counseling

center. Council membership must of course include doctors and/or medical institutions and councils must be involved in intervention within the community as well as in the support of parents and family. Council members have a responsibility to maintain confidentiality, and so the disclosure by medical professionals to a council of personal information believed necessary for protecting a child does not violate the law. Proactive participation in the Councils is required.

### Issues and directions in medical intervention and treatment

The following changes are required in the medical intervention and treatment of child abuse.

#### **Universalization and education of child abuse intervention and treatment**

Intervention and treatment of child abuse has until now been regarded as the role of certain specialists; in the future, however, it will be imperative that general intervention and treatment of child abuse be able to be carried out by anyone, anywhere, in a uniform manner. In other words, the distinction between hospital and doctor must be eliminated and education provided to enable a universal response. At present, interest in child abuse intervention and treatment is gradually growing and taking shape in pediatrics, but awareness is still not high in other fields. The majority of abuse cases involve external injuries that not infrequently require examination at surgeries or emergency care centers. Education about child abuse is required for doctors and other medical professionals in fields that predominantly treat adult patients.

#### **Establishment of hospital systems**

It is unusual for only one medical department or profession alone to treat child abuse. For example, when an infant suddenly stops breathing or has seizures, a pediatrician examines the child and if they suspect a head injury caused by physical abuse, careful examination of the ocular fundus and taking and reading bone survey hopefully by a pediatric radiologist—become necessary. Furthermore, a medical social worker (MSW) and public health nurse are required for cooperation between doctors within and coordination with the resource outside the hospital.

Furthermore, in the intervention of child abuse, doctors and medical professionals tend to hesitate to intervene the child abuse by them-

selves because of 1) feeling guilty for doubting the parents; 2) being fearful of perceived child abuse cases turning out not to have been child abuse; 3) wishing to avoid identifying a problem as child abuse because of the effort involved and the psychological pressure that follows; and 4) having anxiety for making enemy. Therefore, child abuse intervention and treatment systems of the hospital that involve professionals other than the patient's primary physician are very effective. In particular, establishment of a committee lead by senior hospital staff so that decisions are made by not only the primary physician but also the hospital facilitates confronting parents and encourages coordination with resource outside the hospital. It also enables the accumulation of case studies within the hospital and can be expected to improve child abuse intervention and treatment. Such systems are currently being constructed at some university hospitals and children's hospitals. It is recommended that as many hospitals as possible implement such systems.

#### **Construction of a medical system to intervene and to treat child abuse**

For a reasonably large hospital, the hospital system described above could be implemented, but for doctors in private practice and small hospitals, implementation of such methods involve many difficulties. Moreover, in general, all cases of abuse of infants and children up until the age of three require full-body x-rays and examination of the ocular fundus, but only a limited number of hospitals can perform these examinations adequately. Consequently, there is a need for a system in which centralized hospitals that can treat child abuse are established and patients are referred to these in cases where another medical institution suspects child abuse. Currently, even where such systems have been conceived, only a few have actually been established. In future, such a system will need to be established in either each prefecture or each medical care zone.

#### **Promotion of cooperation between organizations**

Collaboration between welfare, health, and education organizations is also important. In many cases this is very difficult for one doctor to achieve. At reasonably sized hospitals, MSW or public health nurses are necessary to enable cooperation with the local community. It is also

recommended that local government bodies establish councils, as described above, to promote child abuse intervention and treatment in local communities. It is vital that medical professionals be included on such councils in order to protect infants, who are especially vulnerable and in danger.

#### **Establishing preventative methods**

Methods of intervention have advanced to some extent, but in comparison, methods for prevention of child abuse and treatment of abused children and their families have been slow. Medical care begun during pregnancy needs to promote the prevention of child abuse, in collaboration with public healthcare, from the gestational or postpartum period. Abuse prevention is particularly necessary from the gestational period onwards in cases such as fetal abuse or denial of the fetus during gestation, DV or other domestic problems, parents feeling no affection for the fetus, or high-risk parents or relatives. For example, precipitate delivery can result in denial of the fetus and presents an extremely high risk for abuse. Despite this, in some such cases mothers and babies are released from hospital without a community network being constructed for them beforehand. The problem here is that there is a strong possibility of the danger of child abuse death being overlooked. It is vital that a community network be created before the mother and child are released from hospital.

#### **Involvement in treatment and care**

Treatment and care of parents who abuse their children and of the abused children themselves is an issue to be faced by the medical field in the future. Medicine is expected to provide the appropriate evaluation of the psychological state of parents that abuse their children and identification of appropriate treatments. However, those treating the abusive parents often developed a parent-centered outlook and may have only low awareness of the need to protect the child. For example, there have been cases in which children have died because healthcare professionals opposed separation of the parents from the children on the grounds that "separation from the children will worsen the parent's condition." The reality of taking the life of their child is a situation that needs to be prevented for the parents' sake, too. Caregivers must be conscious of the fact that care for the parents must also be care for the parents and child.

Children that have been abused tend to have difficulties feeling affection, experience trauma, and suffer interpersonal and behavioral problems. The role required of medical professionals is to evaluate these psychological problems and indicate the direction treatment should take. Treatment of dissociative problems that are common in cases of sexual abuse in particular should be improving.

#### **New specialty**

It is common for the diagnosis of child abuse to require medical specialization. However, knowledge of child traumatology is limited and diagnosis is often difficult. In Japan, there has been a particularly low accumulation of knowledge, and child abuse intervention frequently requires legal procedure. A forensic medicine response is therefore required. Furthermore, as described above, psychological care needs to be established. The specialized nature of abuse medicine needs to be established, research conducted, and knowledge accumulated so that these may be used in intervention and treatment that will ensure that the physical and psychological dangers of abuse to children is avoided. There is a growing need for the establishment of abuse as a specialization and for research by specialists to be promoted.

#### **Child death review team**

In the case of child abuse, the cause of death is frequently given as “non-intended injury.” In

order to prevent child abuse that is hidden in the shadows, it is imperative that all children’s deaths, including accidents, are investigated. In Japan, the Ministry of Health, Labour and Welfare has established a committee to investigate child abuse deaths, making recommendations for investigations in each region.<sup>5</sup> The issue of examining cases of child abuse death is one in which the participation of doctors is vital. The proactive participation of doctors will be vital in the establishment in the near future of regional systems for examining child abuse cases. Furthermore, in the future, it should be critical to establish Child Death Review Team at least in each prefecture.

#### **Feasibility assurance**

Child abuse intervention and treatment requires a tremendous amount of time and specialized knowledge, yet its feasibility is not assured now. Accordingly, the current system becomes increasingly negative as more and more child abuse are identified and addressed. Treating child abuse and protecting the physical and psychological safety of children will help to secure social stability in the future. As long as there is no feasibility assurance in any form, it is obvious that treatment of child abuse in the medical field will plateau; thus measures to counter this are also required. Resolving this problem will lead to the improvement of child abuse treatment in medicine.

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# A Case of Juvenile Temporal Arteritis with Eosinophilia Accompanied with Eosinophilic Vasculitis of Both Lower Legs and Swelling of the Bilateral Inguinal Lymph Nodes

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Taro Mikami,\*<sup>1</sup> Seiko Kou,\*<sup>2</sup> Hiroshi Sakamoto,\*<sup>3</sup> Kuniaki Bando,\*<sup>4</sup> Eriko Takebayashi,\*<sup>5</sup> Hitoshi Komatsu,\*<sup>5</sup> Youichi Iemoto\*<sup>6</sup>

## Abstract

Temporal arteritis (TA) is a disease that usually occurs in the elderly, and its major symptoms include headache, fever, visual impairment, and enlargement of the (superficial) temporal artery. However, a new disease concept, juvenile temporal arteritis with eosinophilia (JTAE), which presents a clinical picture and pathological features different from those of TA, has been proposed in recent years, and case reports of this disease have been increasing. Although patients with this disease usually evidence enlargement of the temporal artery, no conspicuous systemic symptoms are reported to be present. In addition, the histologic features of inflammation of the temporal artery in JTAE are different from those of the giant cell arteritis characteristic of TA.

We experienced a case of JTAE accompanied with vasculitis with eosinophilic infiltration in both lower legs and swelling of the bilateral inguinal lymph nodes. This paper reports this seemingly rare case of JTAE.

**Key words** Juvenile temporal arteritis with eosinophilia, Temporal arteritis, Eosinophilia

## Introduction

Temporal arteritis (TA) usually occurs in the elderly. The major symptoms of this disease include headache, fever, visual impairment, and enlargement of the (superficial) temporal artery.<sup>1,2</sup> However, a new disease concept, “juvenile temporal arteritis with eosinophilia (JTAE),” which presents a clinical picture and pathological features different from those of TA, has been proposed in recent years, and case reports of this disease have been increasing. Although patients with this disease usually evidence en-

largement of the temporal artery, no conspicuous systemic symptoms are present. The features of inflammation of the temporal artery in JTAE are quite different from those of the giant cell arteritis characteristic of TA.<sup>3,4</sup>

We experienced a case of JTAE accompanied with vasculitis with eosinophilic infiltration in both lower legs and swelling of the bilateral inguinal lymph nodes. This paper reports this seemingly rare case of JTAE. The patient’s informed consent was obtained prior to the implementation of various relevant examinations and surgery.

\*1 Department of Plastic and Reconstructive Surgery, Fujisawa City Hospital, Fujisawa; \*2 Department of Plastic and Reconstructive Surgery, Yokohama City University Medical Center, Yokohama; \*3 Division of Collagen Disease, Department of Internal Medicine, Fujisawa City Hospital, Fujisawa; \*4 Department of Neurosurgery, Fujisawa City Hospital, Fujisawa; \*5 Department of Dermatology, Fujisawa City Hospital, Fujisawa; \*6 Department of Pathology, Fujisawa City Hospital, Fujisawa

Correspondence to: Taro Mikami MD, Department of Plastic and Reconstructive Surgery, Fujisawa City Hospital, 2-6-1 Fujisawa, Fujisawa-shi, Kanagawa 251-8550, Japan. Tel: 81-466-25-3111, Fax: 81-466-25-3258, E-mail: ziong@sannet.ne.jp

Table 1 Clinical laboratory findings

	First exam at our hospital	First exam at collagen disease clinic	First exam at dept. of plastic surgery	At lymph node biopsy
WBC [ $/\mu\text{l}$ ]	5,200	8,000	9,000	6,500
RBC [ $\times 10^4/\mu\text{l}$ ]	505	491	538	521
Hb [mg/dl]	16.3	15.7	15.9	15.8
Ht [%]	47.4	48.4	47.9	46.3
Plt [ $\times 10^4/\mu\text{l}$ ]	185	189	169	174
Differential WBC [%]				
Neutrophils	49.3	60.3	58.7	49.6
Lymphocytes	29.7	28.3	18	28.5
Monocytes	4.4	3.3	3.7	7.2
Eosinophils	25.6	7.7	19	14.4
Basophils	1	0.6	0.6	0.3
Total protein [g/dl]	7.5	7.1	7.1	6.9
Albumin [g/dl]	5.1	5.1	4.8	4.6
BUN [mg/dl]	11	8	14	11
Cr [mg/dl]	0.74	0.73	0.82	0.78
AST [IU/L]	18	19	20	20
ALT [IU/L]	17	23	14	15
$\gamma$ -GTP [IU/L]	23	25	18	14
LDH [IU/L]	181		233	
CK [U/L]			203	
Glucose [mg/dl]	93	95	121	
CRP [mg/dl]	0.2>	0.2>	0.2>	0.2>
IgE [IU/L]			1,830	2,010
ESR [mm/hr]		3		

## Case Report

**Patient:** A 25-year-old man.

**Chief complaint:** Funicular node in the bilateral temporal regions and mild headache.

**Past history:** The patient had bronchial asthma in his childhood, but had not had any asthmatic attacks in recent years.

**Smoking history:** Ten cigarettes per day for 5 years (beginning at age 20 and continuing to his current age of 25 years)

**Occupation:** Pet shop employee

**Present illness:** The patient recognized a palpable funicular node in the right temporal region two months prior to the initial medical consultation. He noticed occasional, slight, general malaise, which usually resolved within a few days. He visited a neighborhood doctor and was referred to the department of neurosurgery of our hospital. No particular abnormalities were found in the physical examination.

Blood cell count showed WBC  $5,200/\mu\text{l}$ , and 25.6% eosinophils ( $1,331/\mu\text{l}$ ). CRP was negative. The eosinophilia and the elevated lesion in the temporal region suggested a collagen disease-related condition, and, one month later, the patient was referred to the collagen disease clinic of our hospital.

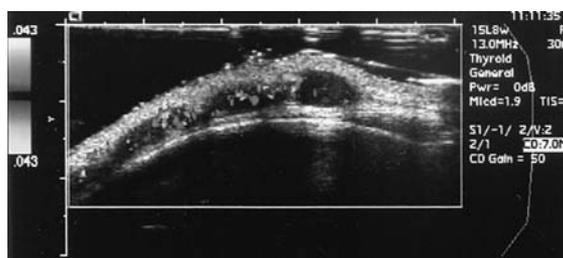
The patient underwent another blood examination including immunological tests. No noteworthy findings, however, were obtained (Table 1).

Three months later, biopsy of the superficial temporal artery was carried out for the purpose of histopathological examination. Light microscopy revealed organizing thrombus and destruction of the arterial wall in some areas, accompanied with marked eosinophilic infiltration. However, the overall histologic picture was different from the one typical of usual temporal arteritis. Trauma-related thrombosis was included in a possible differential diagnosis, and eosinophils seen in the tissue might have represented



**Fig. 1 Contrast CT**

Slight enlargement of the left superficial temporal artery is present



**Fig. 2 Doppler ultrasound**

Enlargement of the frontal branch of the left superficial temporal artery is observed. The branch is partially narrowed, and internal blood flow is inhomogeneous.

a nonspecific response associated with eosinophilia in the blood. The histopathological findings consequently did not lead to a definitive diagnosis. Several months later, a similar condition appeared in the left temporal region. Biopsy of the left superficial temporal artery (temporal branch) was carried out one year after biopsy of the right temporal artery, but no particular differences were noted between the histologic features of the two biopsies.

About two years after the second biopsy, the frontal branch of the left temporal artery began to enlarge, and the patient began to suffer from occasional pain in the area. About four years after the initial onset, the patient was referred from the department of neurosurgery to the department of plastic surgery of our hospital. On initial examination in the department of plastic surgery, a funicular structure about 5 mm in thickness was palpated beneath the skin, slightly anterior to the previous operative scar in the left temporal region. The structure was hard and meandered, providing only slightly palpable beats. Slight rubor was present in the skin, accompanied with mild pressure pain. No bruit was heard upon auscultation. Another blood examination revealed no conspicuous findings other than eosinophilia and a high IgE level (Table 1). Contrast CT of the head showed enlargement of the bilateral superficial temporal arteries alone, consistent with the findings of Doppler ultrasound imaging obtained around the same



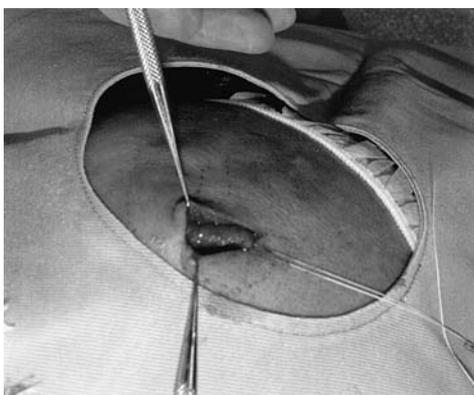
**Fig. 3A Local findings at the time of biopsy**

A prominence is present from the temporal to frontal region

time. There were no other noteworthy findings (Figs. 1, 2).

Biopsy of the left superficial temporal artery was performed under local anesthesia two weeks after the initial examination at the department of plastic surgery.

**Intraoperative findings:** A skin incision was made just above the frontal branch of the prominent superficial temporal artery. A white funicular structure covered with fibrous connective tissue was found just beneath the skin. The structure was detached from the surroundings to a length of about 20 mm and ligated at both ends, and about 15 mm of the tissue was resected. The resected specimen was elastic and hard. A luminal structure was confirmed in the cut end, but the resected portion was almost completely occluded (Fig. 3A, B, C).

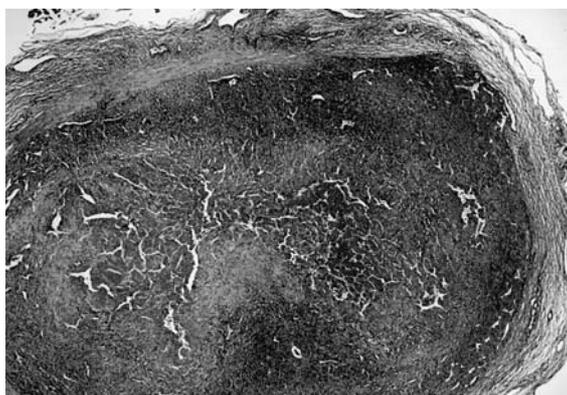


**Fig. 3B** Local findings during resection of the specimen

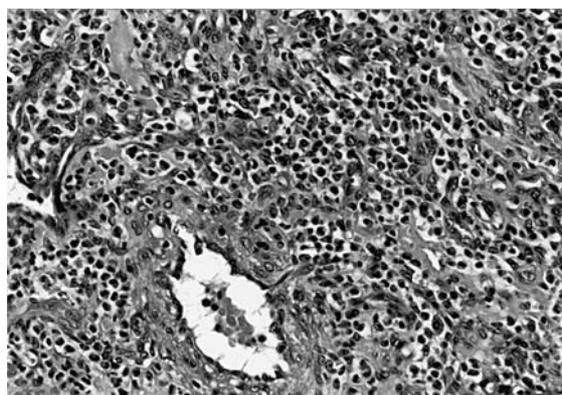


**Fig. 3C** Resected specimen showing a white, hard, funicular structure

The luminal structure was difficult to identify in cross-sections



**Fig. 4** HE-stained section at low magnification shows muscular artery filled with organizing thrombus  
The smooth muscle layer is destroyed in some places



**Fig. 5** HE-stained section at high magnification  
Marked eosinophilic infiltration is present inside the thrombus

**Histopathological findings:** The specimen obtained at the department of plastic surgery was a portion of artery filled with organizing thrombus. The arterial wall was partially destroyed, and elastic fiber and the smooth muscle layer were indistinct. There was marked eosinophilic infiltration (Figs. 4, 5).

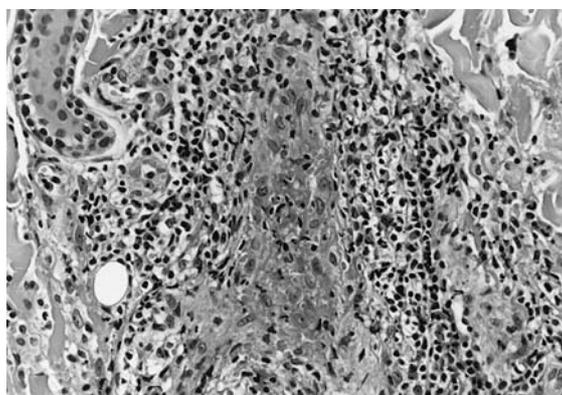
**Course of illness:** The results of histopathologic examination and physical findings suggested JTAE. Since it was expected from previous reports that symptoms would ameliorate without medication, we decided to follow the patient without providing any particular therapy. However, since a detailed occupational history suggested that the handling of vertebrate animals such as cats, dogs, and turtles was associated

with the recurrence of symptoms, we advised the patient to transfer to a different job at his workplace, if possible.

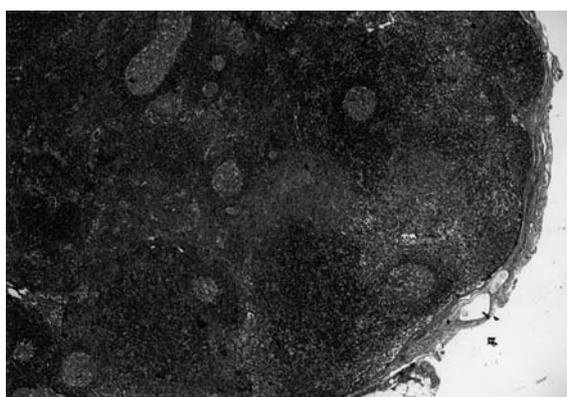
About two months after biopsy of the temporal artery, skin rashes accompanied with itching sensation appeared in both lower legs. The rashes were flat and varied in color tone from florid to dark red, with obscure borders. There were no palpable subcutaneous nodes. Since contact dermatitis was suspected, the patient underwent biopsy at the department of dermatology in our hospital. Histology of the biopsy specimen showed the features of arteritis with eosinophilic infiltration inside and outside microvessels (Fig. 6A, B), suggesting that the skin rashes might



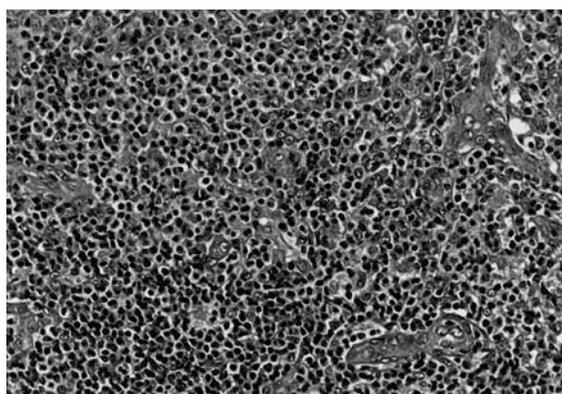
**Fig. 6A Skin rashes on both legs**  
Red rashes with obscure borders are seen in the anterior surfaces of the shanks



**Fig. 6B HE-stained section of the skin rash at high magnification**  
Eosinophilic infiltration is present inside and outside the occluded microvessels



**Fig. 7A HE-stained section of the left inguinal lymph node at low magnification**



**Fig. 7B HE-stained section of the lymph node at high magnification**  
Extensive eosinophilic infiltration is present in the paracortical zone

represent dermal symptoms derived from the arteritis.

Another two months later, a mass measuring 10mm in diameter was palpated in the left inguinal region. Since echography suggested lymph node swelling, biopsy was carried out. There were no specific immunohistological findings, and a diagnosis of nonspecific lymphadenitis was obtained from the findings of light microscopy. However, eosinophilic infiltration was also noted in the biopsy specimen (Fig. 7A, B).

Some time thereafter, the patient transferred to a different job in his workplace, but his symptoms were not relieved for several months. Seven months after the first examination at the department of plastic surgery, the patient suf-

fered temporal pain on a business trip, and visited the collagen disease clinic of a local hospital. Three-day doses of oral prednisolone (25 mg/day) prescribed from the clinic led to improvement of the symptom. Later, suplastat tosilate (300 mg/day) was prescribed from the department of dermatology at our hospital, and since then, the patient's condition has been stable. The patient has had no worsening of the swelling in the temporal region or skin rashes in the lower legs, one year after the first examination at the department of plastic surgery. The patient currently is being followed at a neighborhood

**Table 2 Clinical and pathologic features of juvenile temporal arteritis with eosinophilia**

Epidemiology	Marked predilection for young males
Clinical manifestation	Unilateral or bilateral subcutaneous nodules sometimes accompanied by pain, mimicking the classic temporal arteritis; usually absence of any other signs or symptoms.
Laboratory findings	Hypereosinophilia is sometimes observed; erythrocyte sedimentation rate usually normal
Histopathology	Marked eosinophilic infiltration without giant cells
Evolution	Benign course; does not require oral corticosteroid treatment

(Juvenile temporal arteritis<sup>3</sup>)

**Table 3 Diagnostic criteria of temporal arteritis prescribed by the Ministry of Health and Welfare Study Group for Intractable Diseases (1973)**

<b>A. Major symptoms</b>
1) Headache
2) Visual disorder
3) Inflamed swelling, pain, funicular thickening, and decreased pulsation of the temporal artery
<b>B. Histology</b>
Histologic features of arteritis (giant cell arteritis)
<b>C. Assessment</b>
The diagnosis is definitive if at least one item of the major symptoms is present, accompanied by positive histology. The diagnosis is suspected if at least two items, including the third item as a requisite, of the major symptoms are positive.

(A case of temporal arteritis<sup>8</sup>)

hospital after having relocated to a different workplace.

## Discussion

In 1975, Lie et al. reported in young people a group of temporal arteritis-like disorders different from the usual temporal arteritis and characterized by a lack of systemic symptoms and the histologic features of marked eosinophilic infiltration devoid of giant cells.<sup>3</sup> Since their report documented four cases occurring in 22-, 8-, 7-, and 21-year-old patients, this condition was initially called juvenile temporal arteritis. However, it became apparent after the accumulation of similar case reports that this condition is not necessarily “juvenile,” but sometimes occurred in patients over 50 years of age.<sup>5,6</sup>

In 1996, Fujimoto et al. reviewed 9 cases, including 8 previously reported cases, and named

this condition “juvenile temporal arteritis with eosinophilia (JTAE).”<sup>4</sup> In their report, they described the characteristic clinical symptoms and laboratory findings, including those shown in Table 2. The symptoms of JTAE are different in various aspects from classical temporal arteritis defined by its diagnostic criteria (Table 3), and, therefore, JTAE is now being accepted as an independent disease concept.<sup>5-8,13</sup>

As the pathogenesis of this disease, the possible role of chronic stimulation and trauma<sup>9</sup> or involvement of allergic predisposition have been considered. In addition, some consider that this condition is a subtype of Kimura’s disease,<sup>11</sup> or attribute it to asymptomatic localized polyarteritis nodosa.<sup>3</sup> A case of thromboangiitis obliterans showing eosinophilic infiltration in and complete obstruction of the right temporal artery was also reported as a special case of thromboangiitis obliterans (TAO).<sup>10</sup> A report

of three similar cases has also been found in the literature.<sup>12</sup> It offers worthwhile suggestions as to the mechanisms of occurrence of JTAE, whereas the view exists that JTAE and TAO are pathologic conditions completely different from each other.<sup>4</sup>

Our case was different from previously reported cases of JTAE in the following aspects. First, temporal arteritis occurred on both sides at different times. Second, vasculitis-related skin rashes occurred in the lower legs. Third, concomitant lymph node swelling was present in the inguinal region. However, 2 cases of JTAE accompanied with skin rashes in the lower limbs have been reported by Nitta et al.<sup>6</sup> One of the 2 cases had a record of subcutaneous induration suggestive of lymph node swelling in the inguinal region, although detailed description was lacking. We consider that our present case was consistent with these 2 cases, and this case, although atypical, was diagnosed as JTAE.

The present patient seems to have had a rela-

tively long history of illness. The patient had severe symptoms while handling vertebrate animals in his job, and the symptoms were seemingly improved when he no longer engaged in this work. The patient had a history of bronchial asthma in childhood. Thus, as far as our case is concerned, the mechanisms of JTAE might have been allergic. This speculation is supported by the fact that skin rashes and temporal pain were improved on some occasions by oral adrenocorticosteroid therapy.

Plastic surgeons, including ourselves, more often deal with masses in the facial and cervical regions than doctors of other specialties. It is possible that such patients would visit a department of plastic surgery, presenting with a subcutaneous funicular structure of unknown etiology. Our case is considered to be a case of JTAE. We have reported this case to arouse the attention of plastic surgeons, because up to now no case report of JTAE has been documented in this field.

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# Symptoms and Treatment of Andropause

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Shigeo Horie\*<sup>1</sup>

**Key words** Testosterone, Free testosterone, Andropause, Late onset hypogonadism, Androgen replacement therapy

## Introduction

Hypogonadism is a condition characterized by a lowered blood level of testosterone and complaints of accompanying symptoms. Among the various conditions called andropausal or male menopausal syndromes, the symptom clusters associated with the decrease in testosterone have recently begun to attract much attention. These forms of hypogonadism in relatively old males are more commonly known as “late onset hypogonadism of the aging male” (LOH) in Western countries. Reflecting the upward shift of the retirement age in an aging society, renewed attention has been directed at this condition adversely affecting the QOL of aging males from the standpoint of industrial health.

## Testosterone and LOH

Testosterone is produced by Leydig cells in the testes depending on the stimulation by LH produced in the pituitary gland. Part of the DHEA produced in the adrenal glands is also metabolized to form testosterone. Hypogonadism (hypotestosteronemia) may arise either from low gonadotropin levels or from problems inherent to the testes. In Japan, Iwamoto et al. established the standard values of total testosterone and free testosterone in Japanese adult males. They found that while total testosterone was little affected by aging, free testosterone strongly depended on age and decreased with age (Fig. 1).<sup>1</sup>

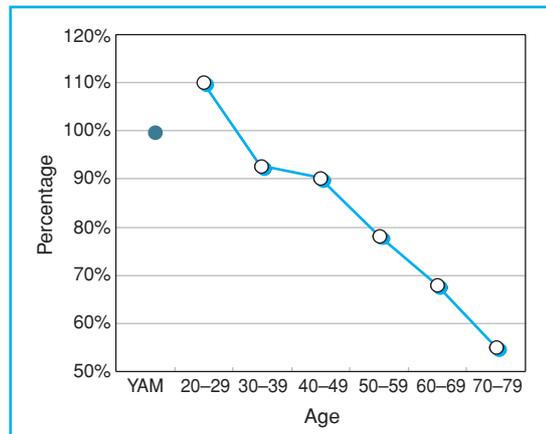
## Symptoms of LOH<sup>2</sup>

The signs and symptoms of LOH include the decline in sexual function, vigor, and the general sense of health, as well as fatigue, depressive symptoms, impairment of cognitive function, lowering of muscle power, muscle and joint pains, decrease in bone density, and anemia. Similarly to menopausal disorders in females, LOH may sometimes present with complaints of autonomic symptoms such as flushing and excessive sweating, as well as feeling of cold in the lower limbs. LOH is usually diagnosed using a symptom questionnaire sheet, in addition to the assessment of the endocrine profile. The Aging Male's Symptoms (AMS) rating score developed by Heinemann (reproduced in Table 1), translated into many languages, is used widely for this purpose. The AMS questionnaire evaluates 17 symptoms on a 5-point scale, and the patient is considered normal if the total score is 26 or less, mild if it is from 27 to 36, moderate if it is from 37 to 49, and severe if it is 50 or more.<sup>3</sup>

## Treatment of LOH

Hypogonadism is treated with androgen replacement therapy (ART). While various testosterone preparations are available internationally in various forms including injections, oral drugs, dermal patches, and gels, Japanese physicians use testosterone almost exclusively in the form of injections. The therapeutic effects of ART include

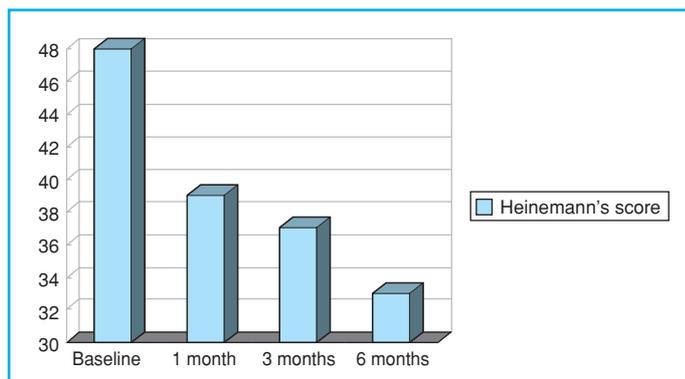
\*1 Department of Urology, Teikyo University School of Medicine, Tokyo  
Correspondence to: Shigeo Horie MD, Department of Urology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan. Tel: 81-3-3964-2497, Fax: 81-3-3964-8934, E-mail: shorie@med.teikyo-u.ac.jp



**Fig. 1** Changes in free testosterone concentration with age  
Free testosterone decreases rapidly with age.

**Table 1** Aging male's symptoms rating scale<sup>3</sup>

AMS Questionnaire						
Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".						
		none	mild	moderate	severe	extremely severe
Symptoms:	Score=	1	2	3	4	5
1. <b>Decline in your feeling of general well-being</b> (general state of health, subjective feeling) .....		<input type="checkbox"/>				
2. <b>Joint pain and muscular ache</b> (lower back pain, joint pain, pain in a limb, general back ache) .....		<input type="checkbox"/>				
3. <b>Excessive sweating</b> (unexpected/sudden episodes of sweating, hot flushes independent of strain) .....		<input type="checkbox"/>				
4. <b>Sleep problems</b> (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness) .....		<input type="checkbox"/>				
5. <b>Increased need for sleep, often feeling tired</b> .....		<input type="checkbox"/>				
6. <b>Irritability</b> (feeling aggressive, easily upset about little things, moody) .....		<input type="checkbox"/>				
7. <b>Nervousness</b> (inner tension, restlessness, feeling fidgety) .....		<input type="checkbox"/>				
8. <b>Anxiety</b> (feeling panicky) .....		<input type="checkbox"/>				
9. <b>Physical exhaustion/lacking vitality</b> (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities) .....		<input type="checkbox"/>				
10. <b>Decrease in muscular strength</b> (feeling of weakness) .....		<input type="checkbox"/>				
11. <b>Depressive mood</b> (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use) .....		<input type="checkbox"/>				
12. <b>Feeling that you have passed your peak</b> .....		<input type="checkbox"/>				
13. <b>Feeling burnt out, having hit rock-bottom</b> .....		<input type="checkbox"/>				
14. <b>Decrease in beard growth</b> .....		<input type="checkbox"/>				
15. <b>Decrease in ability/frequency to perform sexually</b> .....		<input type="checkbox"/>				
16. <b>Decrease in the number of morning erections</b> .....		<input type="checkbox"/>				
17. <b>Decrease in sexual desire/libido</b> (lacking pleasure in sex, lacking desire for sexual intercourse) .....		<input type="checkbox"/>				
<b>Have you got any other major symptoms?</b>	Yes .....	<input type="checkbox"/>		No .....	<input type="checkbox"/>	
<b>If Yes, please describe:</b>						
THANK YOU VERY MUCH FOR YOUR COOPERATION						



**Fig. 2 Changes in aging male's symptoms score before and after ART (Mean of measurements in our patients)**  
ART improves the symptoms score.

improvement of depressive symptoms, decrease in body fat, and increase in muscle power.<sup>4</sup> Major adverse effects are erythrocytosis, sleep apnea, and skin acne. Because the prostate gland is the target organ of DHT, there is concern that ART may potentially promote prostate diseases. The reports available today, however, have shown that ART causes no or very limited increases in the volume of the prostate gland and the level of PSA, a marker for prostate cancer. ART is contraindicated in patients with prostate cancer. Figure 2 shows the mean Heinemann's score before and after ART in our patients. This result indicates that the symptoms score may be used as a surrogate marker for treatment effect.

## Conclusion

The decrease in testosterone levels in aging males represents a pathological condition that deteriorates the QOL of persons at productive ages. In view of the progressive aging of the working population, the need for promoting independence of aged persons, and the increasing relevance of gender-specific medicine, the importance of andrology centered on testosterone metabolism is increasing. We hope to see further elucidation of the actions of testosterone and the development of safer agents for ART.

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