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Pediatric Health Care in the 21st Century

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With the advent of the 21st century, the health care system in Japan has now reached a point where drastic change is required. Various renovations of the health care system have been proposed reflecting the citizens' demands for better health care, issues concerning patient safety, problems concerning the roles of hospitals, the policy of health care containment, and the asserted need for the advanced clinical training program. Important issues that need to be addressed in the field of pediatric health care include the response to the decreasing number of children, the construction of a system for providing pediatric health care including emergency care for children, the understanding and treatment of child psychiatric problems, and the campaigns to protect children from mass media, accidents, etc., as well as the involvement of pediatricians in infant and preschool services to facilitate early intervention aiming at the sound upbringing of children. Although there is an acute shortage of pediatricians, it has been emphasized that the problem lies in manpower available rather than in the nominal number of pediatricians. At present, about 35% of all pediatricians in Japan are women, and the percentage is more than 50% among younger pediatricians. Improvement of the environment supporting the working of female pediatricians is an important factor in constructing the system for providing pediatric health care including emergency care for children.

The provision of pediatric training in the advanced clinical training program is an important means to develop good pediatricians. At present, pediatric training is given as a compulsory subject for a period of 1 to 3 months. Amending the program so that 3-month training will be given as a basic subject, like internal medicine, surgery, etc. is

absolutely essential. It is important to promote the concept that the responsibility of fostering children is shared not only by pediatricians, but also by all physicians. Renovation of the system for certifying specialist pediatricians is required for the improvement of the quality of specialist pediatricians, and efforts are being made toward such renovation. To support the renovation of pediatric health care in Japan according to the global standard, we have been promoting the exchange of opinions and educational campaigns concerning pediatric education and practice in the U.S., Asia, and Europe.

The population of children at the age of 15 or less in Japan has decreased to 13.8% of the national population, and further decreases are anticipated. The sound nurturing of gifted children has become all the more important in this situation. We are now faced with several problems concerning health care and the welfare of children. To build a system to save the lives of children, the Japan Pediatric Society has been making efforts to develop a proposed network of pediatric health care including emergency care for children for several years. The Japan Pediatric Society, the Japanese Society of Child Health, and the Japan Pediatric Association are also working in close cooperation aiming at the enactment of the Child Health Care Law, which would help solve the various problems related to the health care and welfare of children, such as immunization policies, training of pediatricians, and payment of medical costs, as well as the sound growth of children in Japan.

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Clinical Significance of Measuring Lactate Levels in Cord Blood to Predict Development of Respiratory Distress Syndrome in Neonates

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Abstract

Background Reliable measurements of lactate levels as well as blood gas values have become available in the setting of neonatal care. We aimed to evaluate clinical significance of measuring lactate and/or blood gas levels in cord blood associating with perinatal factors and development of respiratory distress syndrome (RDS) that is one of major morbidities in neonates.

Methods Serum lactate levels and blood gas in cord blood were prospectively measured at delivery in an urban maternity hospital.

Results Forty-four cases of RDS were identified in the cohort of 4,881 consecutive neonates. Associations between lactate levels and the 29 clinical variables in the perinatal period were made using multiple linear regression analyses: positive associations with gestational age, abruptio placentae, abnormal presentation and position of the fetus during labor, variable deceleration, late deceleration, prolonged deceleration, early deceleration ($P < 0.001$); negative associations with number of previous deliveries birth weight, Apgar score at 1 and 5 minutes, non-emergent and emergent Cesarean section ($P < 0.001$) as perinatal variables. As a single parameter, lactate could predict occurrence of RDS more accurate than blood gas: pH, base excess, $p\text{CO}_2$, HCO_3^- . However, a model using 29 perinatal parameters was accurate enough to predict development of RDS even without adding data of lactate levels.

Conclusions These results suggest that measuring levels of lactate in cord blood may have some clinical significance but no more than combination of classical perinatal parameters in predicting development of RDS.

Key words Diagnosis, Neonatology, Prediction, Epidemiology, Biostatistics

Introduction

Respiratory disorders manifesting with

tachypnea and other signs such as cyanosis, grunting, nasal flaring, retractions, and decreased breath sounds represent the most frequent cause of admission to neonatal

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intensive care units.¹ A variety of pathological lesions may be responsible for respiratory disorders in neonates, but respiratory distress syndrome (RDS), meconium aspiration syndrome, transient tachypnea of the newborn, and air leak syndrome are the most frequent causes.

RDS occurs primarily in preterm infants, and its incidence is inversely proportional to gestational age and birth weight due to immaturity of the lungs and low production of surfactant.² Recent advances in neonatology have dramatically decreased mortality and morbidity related to respiratory disorders.³ In terms of RDS, early administration of porcine surfactant during brief intubations before the occurrence of serious deterioration reduces the subsequent need for mechanical ventilation and neonatal death.⁴ In addition, low-dose inhaled NO for infants with respiratory illness improves oxygenation and may decrease the risk for chronic lung injury.⁵ Moreover, infants with respiratory disorders who receive early treatment with dexamethasone therapy display improved survival without chronic lung disease compared with infants in whom treatment is delayed.⁶ Thus, an appropriate algorithm to screen neonates at risk for developing respiratory illness just after delivery would thus enable clinicians to select options for early intervention, with a view to reducing neonatal mortality and morbidity further.

The Apgar score has been used to assess the condition and prognosis of neonates worldwide for almost 50 years and remains valid.⁷ However, some investigators have proposed a combination of arterial base excess (BE) in cord blood combined with the Apgar score as a more objective method of assessing newborn adverse events.⁸ Similarly, assessment of both the Apgar score and pH level was shown to improve the accuracy of predicting neonatal mortality in term and pre-term infants.⁹⁻¹¹ Moreover, a growing body of evidence has shown that lactate concentrations in cord blood are good

for predicting neonatal outcome.¹²⁻¹⁴ It is possible that these parameters may be correlated with each other, although optimal predictive combinations of perinatal parameters for RDS have yet to be delineated. Importantly, in recent years, reliable tools for measuring lactate concentrations have become available,¹⁵⁻¹⁷ making lactate and blood gas analysis an interesting option in perinatal care to screen neonates at high risk for developing adverse outcomes.

The present study attempted to evaluate clinical significance of measuring lactate and/or blood gas levels in cord blood associating with perinatal factors and development of respiratory distress syndrome (RDS) that is one of major morbidities in neonates.

Subjects and Methods

Population

Excluding deliveries at home ($n=9$) and intrauterine deaths ($n=27$), a total of 5,096 neonates were born in the Japanese Red Cross Katsushika Maternity Hospital between August 2001 and March 2004. Of these, 213 newborn infants were excluded due to unavailability of cord blood samples for lactate and blood gas measurements. The present study therefore retrospectively examined 4,883 newborn infants. Congenital heart disease was present in 20 neonates, including ventricular septal defect ($n=13$); complete transposition of the great arteries ($n=2$); tetralogy of Fallot ($n=2$); double outlet right ventricle ($n=1$) and coarctation of the aorta ($n=2$). Other congenital anomalies were present in 11 neonates, including esophageal atresia ($n=2$); rectal atresia ($n=2$); hypochondrogenesis ($n=1$); Prader-Willi syndrome with ventricular septal defect ($n=1$), hydrocephalus ($n=2$); hypochondrogenesis with valvular aortic stenosis ($n=1$); sacrococcygeal teratoma ($n=1$); and congenital cytomegalovirus infection ($n=1$). Eight and two neonates displayed trisomy 21 and trisomy 13, respectively. Since newborns with trisomy 13 are usually not able to

survive for long, these two cases were excluded from the following analyses and total 4,881 newborns were studied.

Respiratory distress syndrome

Development of RDS was characterized by noncompliant lungs containing less surfactant than normal, resulting in progressive respiratory distress after birth. Radiological findings on air bronchography and fine reticular granularity of the parenchyma were considered as important findings in diagnosis of RDS.

Perinatal variables

The following perinatal variables were retrospectively retrieved from charts in the hospital and used for multiple regression analysis: (1) age of mother at delivery; (2) number of previous deliveries; (3) gestational age (weeks); (4) birth weight (g); (5) Apgar score at 1 minute; (6) Apgar score at 5 minutes; (7) abruptio placentae; (8) meconium-stained amniotic fluid; (9) oligohydroamnios, defined as an amniotic fluid index ≤ 5 cm; (10) disappearance of baseline fetal heart rate; (11) premature rupture of the membrane, defined as rupture of the membranes before onset of labor at any stage of gestation; (12) cephalo-pelvic disproportion, defined as obstructed labor due to disparity between dimensions of the fetal head and maternal pelvis; (13) placenta previa, defined as location of the placenta over or near the internal os of the cervix; (14) pregnancy-induced hypertension, defined as any new-onset pregnancy-related hypertension; (15) fetal growth restriction, defined as weight below the tenth percentile for gestational age; (16) gender of the neonate; (17) weak pain during labor, defined by uterine dysfunction and characterized by infrequent low-intensity contractions; (18) abnormal presentation and position of the fetus during labor, defined as fetal presentation with the long axis either transverse or oblique, or extension of the head to present the fetal face or brow; (19) vaginal delivery

with cephalic presentation; (20) vacuum extraction/forceps delivery; (21) breech presentation; (22) emergency Cesarean section; (23) non-emergency Cesarean section; (24) twins; (25) forced induction of labor; and (26) variable deceleration; (27) late deceleration; (28) prolonged deceleration; and (29) early deceleration in cardio-tocograph. If there are no signs of deceleration in cardio-tocograph, the state was defined as no bradycardia.

Blood gas and lactate measurements

Cord arterial blood was sampled within 19 minutes (mean \pm SD, 4.3 ± 3.1 minutes) after delivery for routine blood lactate measurement, in addition to blood gas analysis (pH, pCO₂, pO₂, HCO₃⁻, and BE) using an i-STAT® (i-STAT Corporation, East Windsor, NJ, USA) in the delivery room.

Statistical analysis

Difference of lactate, blood gas parameters and perinatal variables between RDS and non-RDS cases were assessed with Student's t-test, Mann-Whitney or chi-square test. The associations between lactate or pH levels in the cord blood and the 29 clinical variables in the perinatal period were determined using multiple linear regression analyses. Diagnostic figures were developed using two statistical approaches: multiple logistic regression models were estimated with the likelihood ratio test and comparisons of area under curve (AUC) of the receiver operator characteristic (ROC) were determined with the chi-square test. All tests were performed to model the probability of RDS development, using STATA 8.0 software (STATA Corporation, College Station, TX, USA).

Results

Summary of lactate levels/blood gas parameters and subjects' characteristics stratified by RDS

Summary of lactate levels and blood gas parameters as well as subjects' characteristics

Table 1A Associations between lactate/blood gas parameters and development of RDS

Variable	Total (n=4,881)	Non-RDS (n=4,837)	RDS (n=44)	P value* ²
Lactate (mmol/L)	3.88 ± 1.69* ¹	3.89 ± 1.69	2.95 ± 2.03	0.0003
pH	7.25 ± 0.08	7.25 ± 0.08	7.28 ± 0.07	0.013
pCO ₂ (mmHg)	50.9 ± 10.6	51.0 ± 10.6	44.4 ± 8.8	<0.0001
HCO ₃ ⁻ (mmol/L)	22.3 ± 2.9	22.3 ± 2.9	21.4 ± 2.9	0.041
BE (mmol/L)	-4.8 ± 3.4	-4.8 ± 3.4	-5.6 ± 3.4	ns* ³

*¹: Mean ± SD *²: Student's t-test *³: not significant**Table 1B Associations between perinatal parameters and development of RDS**

Variable	Total (n=4,881)	Non-RDS (n=4,837)	RDS (n=44)	P value
Age of mother at delivery (years old)	30.7 ± 4.8* ¹	30.7 ± 4.8	30.6 ± 4.3	ns* ⁴
Number of previous deliveries (times)	0.6 ± 0.8	0.6 ± 0.8	0.8 ± 1.0	ns* ⁴
Gestational age (weeks)	38.6 ± 2.3	38.7 ± 2.1	29.9 ± 3.0	<0.0001* ⁴
Birth weight (g)	2,906 ± 540.6	2,920 ± 520	1,418 ± 566	<0.0001* ⁴
Apgar score at 1 minute	8/9/9* ²	8/9/9	5/8/8	<0.0001* ⁵
Apgar score at 5 minutes	9/9/10	9/9/10	7/9/9	<0.0001* ⁵
Abruptio placentae	46	43 (93.5)* ³	3 (6.5)	<0.001* ⁶
Meconium-stained amniotic fluid	764	760 (99.5)	4 (0.5)	ns* ⁶
Oligohydroamnios	120	113 (94.2)	7 (5.8)	<0.001* ⁶
Disappearance of baseline fetal heart rate	27	25 (92.6)	2 (7.4)	<0.001* ⁶
Premature rupture of the membrane	1,187	1,169 (98.5)	18 (1.5)	0.010* ⁶
Cephalo-pelvic disproportion	121	121 (100)	0 (0.0)	ns* ⁶
Placenta previa	50	47 (94.0)	3 (6.0)	<0.001* ⁶
Pregnancy-induced hypertension	259	251 (96.9)	8 (3.1)	<0.001* ⁶
Fetal growth restriction	123	120 (97.6)	3 (2.4)	ns* ⁶
Boys	2,529	2,504 (99.0)	25 (1.0)	ns* ⁶
Weak pain during labor	803	803 (100)	0 (0.0)	0.003
Abnormal presentation and position of the fetus during labor	138	138 (100)	0 (0.0)	ns* ⁶
Vaginal delivery with cephalic presentation	4,525	4,500 (99.5)	25 (0.5)	<0.001* ⁶
Vacuum extraction/forceps delivery	357	357 (100)	0 (0.0)	ns* ⁶
Breech presentation	72	72 (100)	0 (0.0)	ns* ⁶
Emergency Cesarean section	430	406 (94.4)	24 (5.6)	<0.001* ⁶
Non-emergency Cesarean section	583	571 (97.9)	12 (2.1)	0.002
Twin	470	457 (97.2)	13 (2.8)	<0.001* ⁶
Forced induction of labor	1,162	1,162 (100)	0 (0.0)	<0.001* ⁶
Variable deceleration	903	898 (99.5)	5 (0.5)	ns* ⁶
Late deceleration	76	74 (97.4)	2 (2.6)	ns* ⁶
Prolonged deceleration	229	228 (99.6)	1 (0.4)	ns* ⁶
Early deceleration	112	111 (99.1)	1 (0.9)	ns* ⁶

*¹: Mean ± SD *²: 25/50/75 percentile *³: number (%) *⁴: Student's t-test *⁵: Mann-Whitney test *⁶: Chi-square test

were shown in Table 1. Mean lactate levels from 4,881 cord-blood samples were 3.88 ± 1.69 mmol/L (median, 3.57 mmol/L; range, 0.45–17.00 mmol/L), and associations with blood gas parameters were as follows: pH (median, 7.25; range, 6.50–7.52) ($r = -0.017$; $P < 0.001$); $p\text{CO}_2$ (median, 50.9 mmHg; range, 7.1–13.00 mmol/L) ($r = 0.022$; $P < 0.05$); HCO_3^- (median, 22.3 mmol/L; range, 2–35 mmol/L) ($r = 0.383$; $P < 0.001$); and BE levels (median, -4.8 mmol/L; range, -26 – 20 mmol/L) ($r = 0.531$; $P < 0.001$).

Among the 4,881 neonates, 44 (0.90%) developed RDS within 24 hours after birth. Six neonates died during the neonatal period. Three deaths were due to low birth weight with subsequent RDS and sepsis; the other three were due to severe neonatal asphyxia. A further three infants died 1 to 3 months after birth: a low birth-weight infant with chronic lung disease following RDS; an infant born with severe asphyxia with concomitant hypoxic encephalopathy and pneumonia; and an infant found as a near-miss for sudden infant death syndrome at day 2 with subsequent severe brain damage and pneumonia.

Associations of perinatal variables as well as lactate levels and blood gas parameters with development of RDS were made (Table 1A). Lactate levels were significantly lower in RDS newborns than in non-RDS ($P = 0.0003$). If they were stratified by Cesarean section, differences disappeared (data not shown). Levels of pH ($P = 0.0003$) were lower in non-RDS, while levels of PCO_2 ($P < 0.0001$) and HCO_3^- ($P = 0.035$) were lower in RDS than in non-RDS. Levels of BE had no difference between RDS and non-RDS.

A variety of perinatal factors: gestational age; birth weight; Apgar score at 1 and 5 minutes; abruptio placentae; oligohydramnios; disappearance of baseline fetal heart rate; premature rupture of the membrane; placenta previa; pregnancy-induced hypertension; weak pain during labor; cephalic presentation; emergency Cesarean section;

non-emergency Cesarean section; twin and forced induction of labor; had significant associations with development of RDS, as each single variable (Table 1B).

Associations between lactate levels and 29 clinical perinatal variables

Associations between lactate levels and the 29 clinical variables in the perinatal period were made using multiple linear regression analyses (Table 2). Lactate levels had significant positive associations with the following variables: age of mother at delivery ($P = 0.041$); gestational age ($P < 0.001$); abruptio placentae ($P < 0.001$); boy gender ($P = 0.034$); weak pain during labor ($P = 0.022$); abnormal presentation and position of the fetus during labor ($P < 0.001$); vacuum extraction/forceps delivery ($P = 0.016$); variable deceleration ($P < 0.001$); late deceleration ($P < 0.001$); prolonged deceleration ($P < 0.001$); early deceleration ($P < 0.001$). In contrast, lactate levels had significant negative associations with the following variables: number of previous deliveries ($P < 0.001$); birth weight ($P < 0.001$); Apgar score at 1 and 5 minutes ($P < 0.001$); non-emergency Cesarean section ($P < 0.001$) and emergency Cesarean section ($P < 0.001$).

Next, excluding subjects treated with both non-emergent and emergent Cesarean section, associations between lactate levels and the 27 perinatal variables were studied using multiple linear regression analysis. Lactate levels had significant positive associations with the following variables: age of mother at delivery ($P = 0.005$); gestational age ($P < 0.001$); abruptio placentae ($P = 0.020$); cephalo-pelvic disproportion ($P = 0.034$); weak pain during labor ($P = 0.011$); male gender ($P = 0.007$); abnormal presentation and position of the fetus during labor ($P < 0.001$); variable deceleration ($P < 0.001$); late deceleration ($P < 0.001$); prolonged deceleration ($P < 0.001$); early deceleration ($P = 0.001$). On the other hand, lactate levels had significant negative associations with the following variables: number of previous

Table 2 Associations between perinatal variables and levels of lactate in cord blood under multiple regression models

Variable	Total* ¹ (n = 4,881)	Delivery excluding Cesarean section* ² (n = 3,868)	Cesarean section* ³ (n = 1,013)
Age of mother at delivery (years old)	P = 0.041	P = 0.005	
Number of previous deliveries (times)	P < 0.001	P < 0.001	
Gestational age (weeks)	P < 0.001	P < 0.001	P = 0.001
Birth weight (g)	P < 0.001	P < 0.001	
Apgar score at 1 minute	P < 0.001	P < 0.001	P < 0.001
Apgar score at 5 minutes	P < 0.001		P < 0.001
Abruptio placentae	P < 0.001	P = 0.020	P < 0.001
Meconium-stained amniotic fluid			P < 0.001
Oligohydroamnios			
Disappearance of baseline fetal heart rate			
Premature rupture of the membrane			
Cephalo-pelvic disproportion		P = 0.034	Not assessed
Placenta previa			Not assessed
Pregnancy-induced hypertension			
Fetal growth restriction			
Boys	P = 0.034	P = 0.007	
Weak pain during labor	P = 0.022	P = 0.011	
Abnormal presentation and position of the fetus during labor	P = 0.001	P = 0.001	P < 0.001
Vaginal delivery with cephalic presentation			Not assessed
Vacuum extraction/forceps delivery	P = 0.016		
Breech presentation			
Emergency Cesarean section	P < 0.001	Not assessed	Not assessed
Non-emergency Cesarean section	P < 0.001	Not assessed	Not assessed
Twin			P < 0.001
Forced induction of labor			
Variable deceleration	P < 0.001	P < 0.001	P < 0.001
Late deceleration	P < 0.001	P < 0.001	P < 0.001
Prolonged deceleration	P < 0.001	P < 0.001	P < 0.001
Early deceleration	P < 0.001	P = 0.001	

*¹: R² = 0.34 *²: R² = 0.23 *³: R² = 0.50

deliveries (P < 0.001); birth weight (P < 0.001); Apgar score at 1 minute (P < 0.001).

Finally, only focusing on infants borne with Cesarean section either emergent or non-emergent, associations between lactate levels and the 24 perinatal variables in the perinatal period were made using multiple linear regression analyses. Lactate levels had significant positive associations with the following variables: gestational age (P < 0.001);

abruptio placentae (P < 0.001); meconium-stained amniotic fluid (P < 0.001); abnormal presentation and position of the fetus during labor (P < 0.001); twin (P < 0.001); late deceleration (P < 0.001); prolonged deceleration (P < 0.001). Lactate levels had significant negative associations with the following variables: Apgar score at 1 and 5 minutes (P < 0.001).

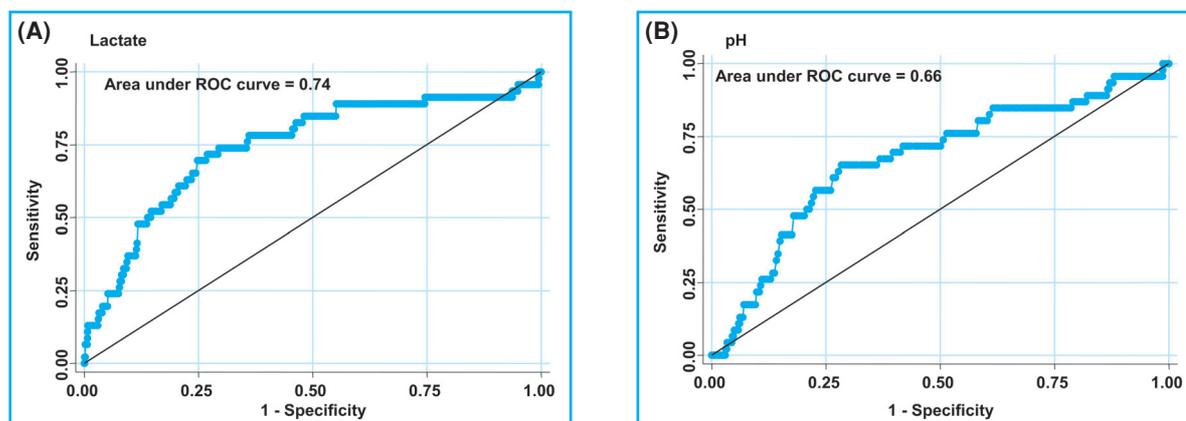


Fig. 1 ROC curve analysis for RDS by lactate (A) or by pH (B)

Receiver operating characteristics (ROC) curve analysis

The AUC of the ROC to detect RDS by lactate: 0.74 (95% confidence interval [CI]: 0.65 to 0.82) (Fig. 1A) was significantly higher ($P < 0.0001$) than that by pH: 0.66 (95% CI: 0.57 to 0.74) (Fig. 1B). Other blood gas parameters: base excess, $p\text{CO}_2$, HCO_3^- did not have significant predictive value.

The AUC of the ROC to detect RDS using the 29 variables was high: 0.992 (95% CI: 0.986 to 0.997) (Fig. 2). When lactate levels were added to the model, the AUC significantly increased to 0.993 (95% CI: 0.987 to 0.998) ($P = 0.0017$). On the other hand, none of the blood gas parameters (pH, PCO_2 , BE, or HCO_3^-) significantly improved the accuracy of the AUC. Moreover, the addition of these four blood gas parameters to lactate and the other 29 perinatal variables did not significantly improve the AUC of lactate and the other 29 perinatal variables.

Discussion

We demonstrated that levels of lactate in cord blood were associated with a variety of perinatal factors. Duration of the active second stage of labor was shown to be significantly associated with fetal and maternal

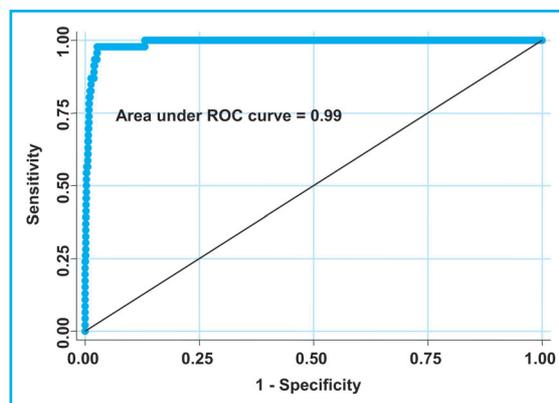


Fig. 2 ROC curve analysis based on multiple logistic models for RDS using 29 variables

lactate levels at crowning of the fetal head, and lactate levels in umbilical arterial and venous blood at delivery,¹⁸ suggesting that lactate levels may reflect difficulties in the active second stage of labor, at least in part. In fact, associations of lactate levels with the age of mother at delivery, the number of previous deliveries, gestational age, abruptio placentae, cephalo-pelvic disproportion, abnormal presentation, position of the fetus during labor, twins and non-Cesarean births were confirmed in this study, which may support the hypothesis that difficulties seen during prolonged delivery times may raise levels of lactate in cord blood. On the other hand, associations

with deceleration in cardio-tocograph, birth weight, and Apgar score in this study suggest that asphyxic stress to the fetus itself may also raise levels of lactate.

In the late 1990s, the clinical significance of lactate levels in cord blood was suggested to be associated with adverse pathophysiology of newborns,¹⁹ and be superior to the Apgar score in assessing neonatal function.²⁰ Specifically, measurement of lactate levels in cord blood was reported to be useful in hypoxic ischemic encephalopathy,^{21,22} and other diseases,²³ but not in RDS. As a single variable, lactate levels as well as blood gas parameter: pH; pCO₂; HCO₃⁻; showed significant association with development of RDS. However, lactate levels in cord blood were significantly lower in neonates who developed into RDS later, which was unexpected. Both lactate levels and risk of RDS can be confounded by perinatal factors, which make difficult to evaluate clinical importance of measuring levels of lactate in cord blood. Therefore, we conducted multiple regression analysis to know adjusted clinical significance of lactate levels in predicting development of RDS.

Factors such as gestational age and mode of delivery have been shown to predict RDS or other respiratory diseases in neonates.^{24,25} In addition, the combination of the Apgar score with cord arterial blood pH levels was shown to predict adverse events in neonates.²⁶ In this study, lactate levels was also shown to improve the accuracy of the

model using multiple regression analysis that used 29 perinatal parameters including the Apgar score, gestational age, and Cesarean section. However, the accuracy of the model using perinatal variables even without lactate levels in cord blood was already high enough to predict development of RDS. Thus, measuring of lactate levels and blood gas parameters may have minor clinical significance in knowing occurrence of RDS. In other words, classical perinatal variables still have clinical importance.

This study specifically used a variety of perinatal parameters including lactate levels. The number of newborns enrolled in this study in whom lactate and other blood gas variables were measured and available was greater than previous articles, which allowed us to perform statistical analyses using a variety of parameters. This could further overcome confounding by perinatal parameters. However, the small number infants with RDS may have lowered clinical significance of measuring lactate levels.

In conclusion, measuring levels of lactate in cord blood may have some clinical significance but no more than combination of classical perinatal parameters in predicting development of RDS.

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Activation of Indoleamine 2,3-Dioxygenase in Children with Acute Febrile Diseases

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Abstract

Background The clinical severity of acute inflammatory diseases may be worsened by tissue injury triggered by oxidative stress. Indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan (TRP) to kynurenine (KYN), is known to be an antioxidant, but its kinetics during the acute febrile phase in children have not been delineated.

Methods We retrospectively measured serum TRP, KYN, and vitamin A/E concentrations as well as C-reactive protein (CRP) levels in 89 children with acute febrile disease (n = 62) and afebrile chronic disease (n = 27). Next, the protective effects of vitamin A on IDO activity were studied using phytohemagglutinin (PHA)-stimulated human mononuclear cells (MCs) in vitro.

Results Serum levels of TRP and the ratio of TRP/KYN were significantly lower in febrile children than in afebrile children (P < 0.0001) and in PHA-stimulated MCs than non-stimulated cells (P < 0.0001). There was positive linear relationship between serum levels of vitamin A and TRP (P < 0.001) in children who were CRP positive (CRP ≥ 0.5 mg/dL). However, changes in TRP/KYN triggered by PHA were not altered by the addition of vitamin A.

Conclusions These results suggest IDO activity may be stimulated in children with acute febrile diseases.

Key words Tryptophan, Kynurenine, IDO, Infectious disease, Children

Introduction

Oxidants produced during inflammation contribute to cell and tissue damage either directly or through the activation of proteases.¹ For example, influenza virus triggers an oxidant stress response in the lungs that induces pneumonia.² However, free radicals at the sites of inflammation can be removed by antioxidant defenses, including catalase, glutathione peroxidase, superoxide dismutase, and vitamins A, C, E as well as reactive oxy-

gen species including nitric oxide and related species.^{3,4} Specifically, antioxidants have been shown to reduce the severity of asthma by inhibiting tissue damage.⁵ In addition, plasma levels of specific carotenoids have been shown to be significantly lower in children with cystic fibrosis than in normal subjects,⁶ which suggests that antioxidants may be consumed, which destroy toxic oxygen species in inflammatory states.

In particular, treatment with vitamin A reduces morbidity and mortality associated with measles independent of nutritional

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deficiency.⁷ In addition, in areas where vitamin A deficiency and malnutrition are documented public health problems, the regular provision of vitamin A supplements to children, at a level potentially obtainable from foods, was shown to contribute substantially to children's survival: overall mortality was reduced on average by 54%.⁸ Thus, at least in part, supplementation with vitamin A and related products may play an important role in reducing complications from infectious diseases in children by acting as an antioxidant. However, the kinetics of vitamin A during the acute phase of common infectious diseases remains uncertain in developed countries.

In addition to vitamin A, indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme that catabolizes tryptophan (TRP) to kynurenine (KYN),⁹ works as one of the major antioxidants preventing oxidative damage to host tissue during inflammation.^{10,11} The activity of IDO apparently increases more than 100-fold in the lungs of mice infected with the influenza virus.^{12,13} However, the metabolism of TRP in relation to IDO activity remains uncertain in the serum of patients in the acute phase of an infectious disease.

In this study, we retrospectively measured the concentrations of TRP/KYN to study the enzymatic activity of IDO in serum from children with a variety of acute or chronic pediatric diseases, and compared findings between children in febrile and afebrile states. Moreover, associations between TRP/KYN and vitamin A were examined in vivo and in vitro.

Subjects and Methods

Population

This study was approved by institutional review board of Yokohama General Hospital. A total of 146 children visited a community hospital between September 2002 and December 2002 and underwent blood tests including C-reactive protein (CRP) for clinical

purposes. Of these, 57 children were excluded from this study because serum samples were not kept. The present study therefore retrospectively examined extra volume serum samples derived from 89 patients. The patients were categorized as febrile when they complained of fever of more than 38.0 centigrade.

Preparation of blood-derived mononuclear cells for in vitro experiment

Heparinized peripheral blood (50 mL) was obtained from five independent healthy adult volunteers. Mononuclear cells (MCs) were isolated from the blood by centrifugation on a Ficoll-Paque density gradient (Amersham Biosciences, Uppsala, Sweden). Cells were cultured for 14 days in 90% RPMI1640 with L-glutamine/streptomycin-penicillin and 10% fetal bovine serum at 37°C in a humidified 5% CO₂ atmosphere at 1.0 × 10⁶/mL in 1 mL, with or without phytohemagglutinin (PHA) (1 mg/mL) (Sigma Chemical Co. Ltd., St. Louis, MO, USA), with or without vitamin A (25, 50, 100 μg/dL) (Sigma Chemical Co. Ltd.) plus vitamin A binding protein (1 mg/mL) (Sigma Chemical Co. Ltd.).

High-pressure liquid chromatography (HPLC) determination of TRP/KYN and vitamin A/E

Total free TRP and KYN were quantified in serum or culture media by HPLC as previously described.¹⁴ Similarly, serum levels of vitamin A and vitamin E were measured with HPLC.¹⁵

Statistical analysis

Levels of TRP and KYN, the ratio of TRP/KYN, as well as vitamin A and vitamin E levels were compared between afebrile and febrile patients using the Student's t-test. Linear regression analysis was performed to determine any association between the two parameters. A p-value of 0.05 was considered significant. All tests were performed using STATA 8.0 software (STATA Corpo-

ration, College Station, TX, USA).

Results

Patients' characteristics

Of the 89 children included in the study, 51 were male and 38 were female. The mean age of patients was 5.3 ± 4.6 years. Sixty-two patients were in a febrile condition due to an infectious disease, including antigen-confirmed influenza ($n=11$); croup, bronchitis, bronchiolitis, or pneumonia ($n=24$); viral gastroenteritis ($n=10$); measles or mumps ($n=4$); other conditions ($n=13$). Twenty-seven patients were afebrile but had non-infectious diseases, including bronchial asthma and/or atopic dermatitis ($n=9$);

epilepsy ($n=3$); liver dysfunction ($n=2$); other conditions ($n=13$).

Differences in serum measures between afebrile and febrile patients

The means \pm standard deviations for the various variables measured in the 89 patients were as follows: TRP = $35.3 \pm 11.2 \mu\text{M}$; KYN = $2.3 \pm 0.9 \mu\text{M}$; ratio of TRP/KYN = 17.8 ± 8.3 ; vitamin A = $20.9 \pm 10.8 \mu\text{g/dL}$; vitamin E = $6.9 \pm 2.0 \mu\text{g/dL}$; CRP = $1.3 \pm 2.5 \text{ mg/dL}$. Serum levels of TRP and the ratio of TRP/KYN were significantly lower in febrile children than in afebrile children ($P < 0.0001$), whereas KYN levels were not significantly different between the two groups (Fig. 1).

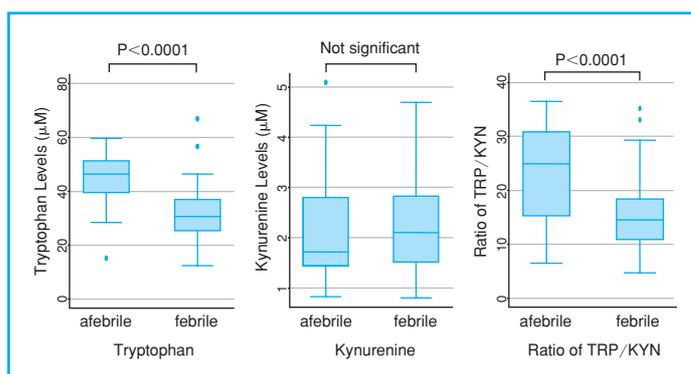


Fig. 1 Difference in serum levels of TRP, KYN and ratio of TRP/KYN between afebrile and febrile patients
Student's t-test was performed and p-values are shown.

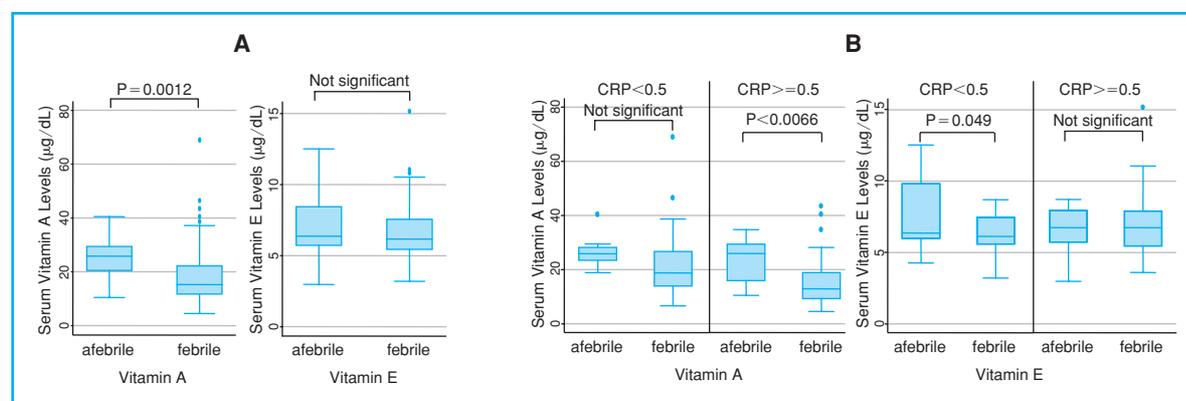


Fig. 2 Difference in serum levels of vitamin A and vitamin E between afebrile and febrile patients

Student's t-test was performed and p-values are shown.

(A) Not stratified by CRP, (B) Stratified by CRP: CRP was negative ($< 0.5 \text{ mg/dL}$); CRP positive ($\geq 0.5 \text{ mg/dL}$).

Serum levels of vitamin A were significantly lower in febrile children than in afebrile children ($P=0.012$); however, vitamin E levels were not significantly different between the two groups (Fig. 2A). Patients were then further stratified by whether they had negative or positive CRP levels (CRP negative, <0.5 mg/dL; CRP positive, ≥ 0.5 mg/dL) (Fig. 2B). Levels of vitamin A significantly decreased in febrile children who were CRP positive ($P=0.0066$). In contrast, levels of vitamin E significantly decreased in febrile children who were CRP

negative ($P=0.049$).

Associations between vitamin A and TRP/KYN levels

In children who were CRP positive, there was a positive linear association between serum levels of vitamin A and TRP ($P<0.001$); no significant association between these values was detected in children who were CRP negative (Fig. 3). Similarly, in children who were CRP positive, there was a positive linear association between serum levels of vitamin A and the ratio of TRP/

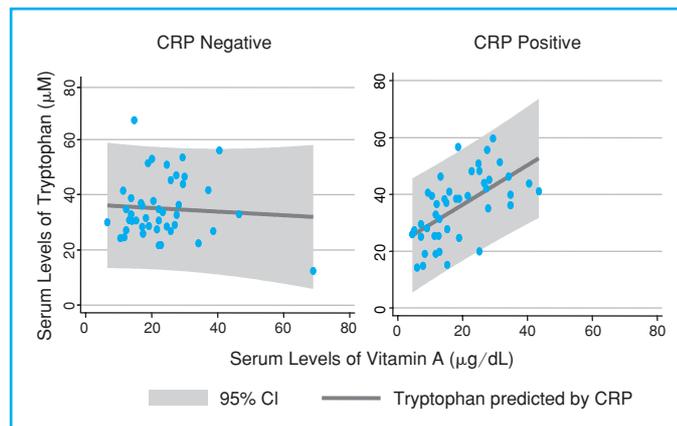


Fig. 3 Scattered plot showing association between serum levels of vitamin A and tryptophan stratified CRP
Dots: Observed. Line: Predicted value with 95% confidence intervals.

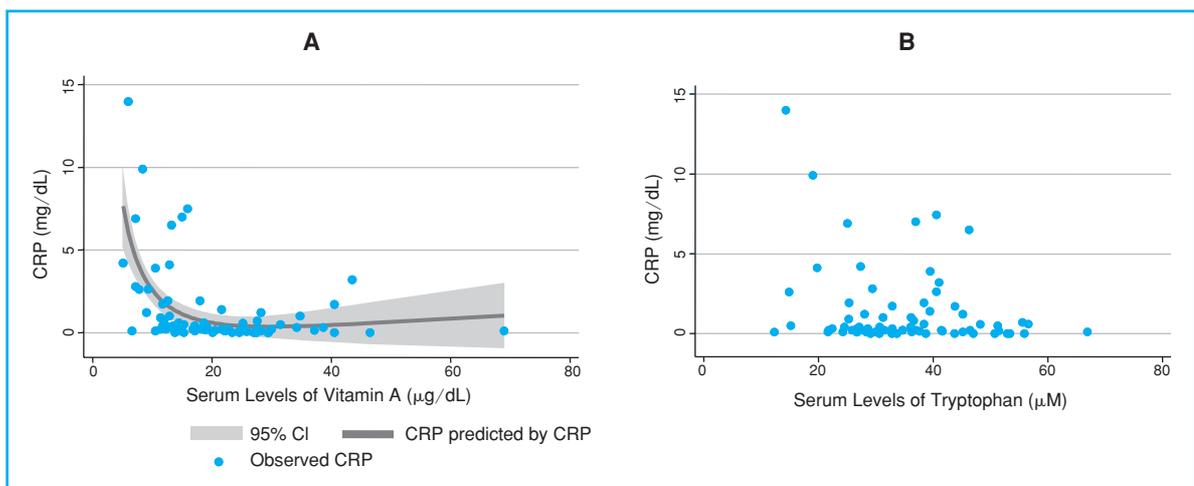


Fig. 4 (A) Scattered plot showing associations between serum levels of vitamin A and CRP
(B) Scattered plot showing associations between serum levels of tryptophan and CRP
Dots: Observed. Line: Predicted value with 95% confidence intervals.

KYN ($P=0.015$); no significant association was seen in children who were CRP negative. No significant associations between vitamin A and KYN were seen. Serum levels of vitamin E were not significantly associated with TRP or KYN levels or the ratio of TRP/KYN.

Associations between vitamin A and CRP levels

Serum vitamin A levels had a significant and inverse association with CRP levels (Fig. 4A). Specifically, when vitamin A levels were above $20\mu\text{g/dL}$, no child had a CRP level higher than 4 mg/mL . In contrast, there was no significant association between TRP and CRP levels (Fig. 4B). Neither KYN nor the ratios of TRP/KYN were associated with CRP levels (data not shown).

Effects of PHA on metabolism of TRP and KYN and the ratio of TRP/KYN

Supernatants of mononuclear cells stimulated with PHA contained significantly lower TRP levels as well as a lower ratio of TRP/KYN and significantly higher KYN levels than non-stimulated cells, ($P<0.0001$) (Fig. 5). Levels of TRP, KYN, and the ratio of TRP/KYN were not altered by the addition of vitamin A and vitamin A binding protein (data not shown in Fig. 5).

Discussion

Serum levels of TRP and the ratio of TRP/KYN were significantly lower in febrile children than in afebrile children. Moreover, stimulation of mononuclear cells with PHA in vitro remarkably decreased TRP levels and the ratio of TRP/KYN while increasing KYN levels. These findings suggest that non-specific stimulation of the immune system may facilitate metabolism of TRP to KYN, which correlates with activation of IDO both in vivo and in vitro. Increased concentrations of KYN have been reported during febrile convulsions,¹⁶ suggesting that enhanced TRP metabolism during febrile conditions in children may trigger convulsions.

Levels of vitamin A significantly decreased in febrile children who were CRP positive; this decrease was not seen in children who were CRP negative. Previous reports have shown that serum retinol and retinol binding protein concentrations fall in periods of infection.¹⁷ Similarly, levels of acute-phase proteins have been shown to have an inverse relationship with vitamin A concentrations in children.^{18–20} These findings are consistent with our results. In children who were CRP positive, there was a positive linear association between serum levels of vitamin A and TRP as well as the ratio of TRP/KYN; how-

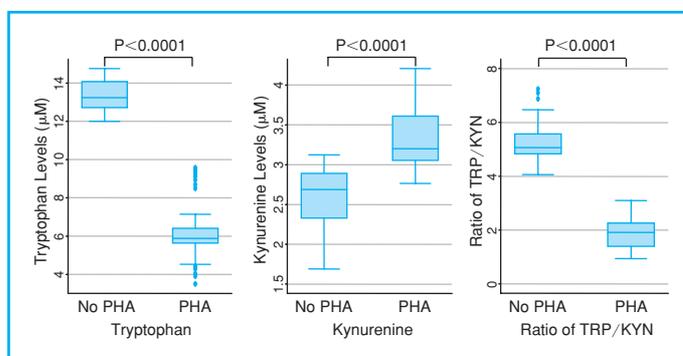


Fig. 5 Effects of PHA on metabolism of tryptophan, kynurenine and ratio of tryptophan/kynurenine
Mononuclear cells derived from five independent adults were cultured for 14 days in 90% RPMI1640 with 10% FBS at 37°C with or without PHA. Lower ratio of TRP/KYN suggests activation of IDO.

ever, no significant association between these variables was detected in children who were CRP negative. The addition of vitamin A did not affect the metabolism of TRP in this study. To our knowledge, there are no reports that describe the association between vitamin A and TRP metabolism. Our findings suggest the reduction of vitamin A levels and facilitation of IDO-related metabolism may be an independent phenomenon following

pro- and inflammatory reactions.

These results suggest that IDO activity may be stimulated in children with acute febrile diseases.

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Japanese National Strategic Plan for Medical Care and Maternal and Child Health Care

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Abstract

The purpose of this paper is to examine our National Strategic Plan for Medical Care, as put forth in 1985 (modified in part in 2003) by the Medical Care Act, from the perspective of maternal and child health care, and to propose a new plan of action in maternal and child health care for the 21st century.

The National Strategic Plan for Medical Care consists of four major domains of medical services, general medicine, psychiatric medicine, infectious diseases, and tuberculosis, to provide the nation (52 tertiary medical care areas and 369 secondary medical care areas) with basic medical resources in each domain. The inherent weakness of the plan is the neglect of maternal and child health care, since the vast majority of the target populations are elderly and children are in the minority. Further, there are a number of complex co-morbidities in children and families that are under-addressed.

To address maternal and child health appropriately in practice, the National Strategic Plan for Medical Care needs to be rewritten with the following four new major domains of medical services being women of reproductive age, children, adults, and elderly.

Key words Japanese health policy, Child health care, Tertiary medical care, Secondary medical care, Medical Care Act

Introduction

The Medical Care Act was first established in 1948 when Japan was recovering from postwar destruction to address the nation's commitment to universal access to health care and the availability of health care personnel and facilities for all the residents. It has remained in effect for more than half a century, although minor revisions have been made several times. The Medical Care Act is the basis of the National Strategic Plan for Medical Care that determines the framework for health care and availability of health care

personnel and facilities throughout the country. The latest plan was compiled in 2003 by the Ministry of Health, Labor and Welfare and was delivered as an official notice of the Director, Bureau of Health Policy, Ministry of Health, Labor and Welfare (MHLW), transmitting the national government's decisions down the organizational hierarchy to all 47 regional governments.

In this paper, we provide critique of the National Strategic Plan for Medical Care from the perspective of maternal and child health care and show that health care for women and children is not adequately addressed and that the various national

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guidelines are essentially irrelevant to maternal and child health. We then propose a new scheme of the National Strategic Plan for Medical Care to allocate more equitably the resources for women of reproductive age, children, adults, and elderly.

The National Strategic Plan for Medical Care

The master plan for medical care in Japan is based on the National Strategic Plan for Medical Care stipulated in the Medical Care Act (Articles 30-3 through 30-7, as amended in 1985). According to this Law, the governor of each prefecture must prepare a health care plan for the prefecture and submit it to the Minister of Health, Labor and Welfare. The 1986 Notice of Director of Health Policy Bureau, MHLW, entitled “Regarding Medical Strategic Plan”, suggested subject headings for required documentation in the prefectural health plan: (1) general discussion (optional), (2) the assessment of the present status of the prefecture (optional), (3) topography of the prefectural health care system (mandatory), (4) necessary number of beds in the region (mandatory), (5) perspective for medical resources in the region and action plan (optional).

The optional items in the above list were made mandatory by the 1998 Notice of Director of Health Policy Bureau, MHLW, entitled “Regarding Medical Strategic Plan” and “Medical Care Plan Development Guidelines” which were issued in response to the partial amendment of the Medical Care Act in 1998. This amendment emphasized further systematization of regional health care and demanded that the national government provide more detailed guidance to prefectures.

Organization of the National Strategic Plan for Medical Care

The text of the National Strategic Plan for Medical Care lacks a general discussion, given its absence in the Medical Care Act.

Article 30-3 of the Medical Care Act lists itemized specific mandates for the prefectural health care plan. At the beginning of Article 30-3, the Law states, “Each prefecture shall define the plan for organizing health care in the region”. Article 30-3-2 then stipulates Items 1 through 9 that should be determined by each prefecture. In brief, these 9 items required each prefecture to define medical service or health care areas (secondary-tertiary care), regulate the number of beds, secure the number of health care professionals, and organize comprehensive health care system. Articles 30-3-3 to 30-3-13 and Articles 30-4 to 30-7, supplemented by the Medical Strategic Plan Development Guidelines, are also examples of detailed governmental regulations.

The Medical Care Plan Development Guidelines (Official Notice of Health Policy Bureau, MHLW) states, “The health care plan developed by the prefecture shall contain description of goal and scope of the plan”, but the national government does not provide any in the National Strategic Plan for Medical Care.

Governmentally defined health care areas

While the term “health care area” is not used in the text of the Medical Care Act, secondary-tertiary care concepts are described in Articles 30-3-2-1, 30-3-2-2, 30-3-3, and 30-3-4 of the Law. Although the description of the text is ambiguous, it appears that Article 30-3-2-1 refers to secondary care areas and Article 30-3-2-3 refers to tertiary care areas. However, the concept of primary care areas is not described in the text of the Law. The reason that the Law does not define primary care areas is not clear.

The term “health care area” is used in Item 3-3 of the Medical Care Plan Development Guidelines (1985). While this document also makes no mention of primary care areas, a secondary care area is defined as an area established to meet general health care needs excluding more specialized clinical expertise, and a tertiary care area is defined

as an area established to meet special health care needs. However, the secondary and tertiary health care areas, as defined here, are applicable to only adults, leaving children out of the scope.

The reference to children was first made in the context of secondary care area in 1998 in the Medical Care Plan Development Guidelines (Item 3-3-1). The original description was amended to read, “In addition, sufficient consideration shall be given to the mental health care and pediatric health care in the planning of the secondary care areas. Although not sufficiently addressed, the need for organization of secondary care for children began to be recognized in 1998 as an

important issue by the national government.

The resources for the secondary and tertiary care for children are essentially different from those for adults: human resources, medical facilities, equipments, etc. The need for health care resources also differ among children of different age groups (neonates, infants, school children, and adolescents), as well as among various specialized disciplines. Typical examples include a NICU for extremely low birth weight infants and a mental health care unit for children and adolescents.

One important difference between adult and pediatric health care is reflected by the routine division of adult health care into

Table 1 Tertiary and sub-tertiary care areas within prefectures

(researched by the present authors, December 2003)

Prefecture	Tertiary care area and sub-tertiary care area	Population of children under 15 years of age	Number of self-designated pediatricians	Number of self-designated pediatricians per 100,000 population of children under 15 years of age
Hokkaido	South	67,208	54	80.3
	Central	455,696	378	83.0
	North	90,861	97	106.8
	Okhotsk	45,796	25	54.6
	Tokachi	53,497	25	46.7
	Kushiro & Nemuro	52,500	29	55.2
Nagano	East	63,591	40	62.9
	South	85,132	47	55.2
	Central	77,540	108	139.3
	North	99,060	51	51.5
Akita	North	35,167	20	56.9
	Central	76,749	84	109.4
	South	45,156	21	46.5
Niigata	North	227,733	174	76.4
	Central	88,664	63	71.1
	South	37,630	20	53.1
Ehime	East	74,069	58	78.3
	Central	96,048	100	104.1
	South	43,292	27	62.4
Fukushima	Central	194,419	143	73.6
	Aizu	48,521	30	61.8
	Coastal	87,573	43	49.1

physical health care (general beds) and mental health care (psychiatric beds); however, such a distinction is problematic in the case of pediatric health care. The body and mind of a child is so closely interconnected and often inseparable. Child abuse and eating disorders are such examples, and both physical and mental health care needs must be addressed together. We believe that the separation of general beds and psychiatric beds in adult health care is not useful in child health care.

Item 4-5 of the Medical Care Plan Development Guidelines in 1985 provided for 1) promotion of primary care and 2) coordinated primary-secondary-tertiary care. Note that “primary care” in the Japanese text is a phonetic transcription from English, while actual Japanese terms are used to denote secondary and tertiary care; the reason for this wording is unknown. Furthermore, the relationship between primary care and primary care areas is not clarified in the text.

Total number of primary care areas is not defined. As of September 2003, there are 369 secondary care areas and 52 tertiary care areas. A tertiary care area generally corresponds to a prefecture, but Hokkaido is divided into 6 tertiary care areas because of its wide geographical area. Hence, the total number of tertiary care area is officially defined to be 52 (one each in 46 prefectures plus six in Hokkaido prefecture).

There are at least five more prefectures that modified the above rule, in practice, at the prefectural level. Nagano Prefecture has four tertiary care areas within the prefecture in addition to the one covering the whole prefecture. Akita, Niigata, and Ehime Prefectures each have 3 sub-tertiary care areas. (Term “sub-tertiary care area” seems to have been introduced by the personnel of one of these 3 prefectures, but the definition of this obscure term is not provided). Fukushima Prefecture proposes 3 areas that may be regarded as tertiary care areas (Table 1).

Whatever the terminology may be, the above-mentioned 6 prefectures use a basic

structure in which a prefecture is divided into multiple (3 to 6) areas that function as tertiary care areas. As indicated by this practice, the concept of “one tertiary care area in one prefecture” set by the national government is losing practical relevance. In view of the rapid advancement and specialization in the medical services, the response of each prefecture is understandable, but we need to reconsider the concept of tertiary care and tertiary care areas from global perspectives. We need to address the effective utilization of limited medical resources using larger geographical units, not necessarily confined to the present prefectural boundary. A basic structure in which each tertiary care area consists of several prefectures may be a reasonable possibility. The national government and regional governments need to work in concert to overcome undue regulation and prefectural egoism toward rational regionalization of health care.

Number of beds in the region

Article 30-3 “Medical Strategic Plan” of the Medical Care Act stipulates the number of beds necessary in secondary care area in each of four categories: general beds (including chronic care beds), psychiatric beds, infectious disease beds, and tuberculosis beds (While the amendment of the Medical Care Act in December 2000 replaced the term “necessary number of beds” with “standardized number of beds”, we use the former in this paper because the meaning is clearer).

The number of beds in each secondary care area is calculated by the formula shown below. Although the meaning of the formula and its variables seem self-explanatory, the government’s provisions are not readily understandable because they contain many arbitrary modification rules.

The number of beds in a secondary care area = $\frac{\sum AB + C - D}{E} \times F$, where

A: population of the secondary care area by sex and age group;

B: sex and age group specific hospitalization

- rate in the secondary care area;
- C: number of hospitalized patients incoming to the secondary care area;
- D: number of hospitalized patients outgoing from the secondary care area;
- E: bed utilization rate, 0.84 (fixed across the nation); and
- F: adjustment coefficient for the average length of stay, 0.9 (fixed across the nation).

To be more precise, “population” refers to the nighttime population, and “age group” refers to 5-year age group as based on the latest census data, and “hospitalization rate” refers to one of 3 different figures: 1) prefectural, 2) regional (see below), and 3) nationally standardized (arbitrarily defined by MHLW). The national government will recommend one of the 3 hospitalization rates for the prefectural government to apply it to each secondary care area. Table 2 shows arbitrary hospitalization rates by sex and age-group set by MHLW (the 2001 Notifi-

cation #22). “Region” refers to a region of several prefectures. There are 9 regions; Hokkaido (1 prefecture), Tohoku (6 prefectures), Kanto (10), Hokuriku (3), Tokai (4), Kinki (6), Chugoku (5), Shikoku (4), and Kyushu (8) (Table 3). The numbers of “incoming patients” and “outgoing patients” are estimated from a national survey data on patients and a national survey data on receipts used in health insurance systems. The “bed utilization rate” is fixed at 0.84 across the country by the 2001 Notification #22 of MHLW. The “adjustment coefficient” for the average length of stay is similarly fixed at 0.9 across the country by the 2001 Notification #22 of MHLW. The Notice of the Director, Health Policy Bureau, MHLW issued in June 1998 states that Minister of Health, Labor and Welfare determines “adjustment coefficient” taking into consideration the average length of stay at the time. The Notice has made no further explanation, however.

Table 2 Nationally standardized hospitalization rate by sex and age group as defined by MHLW
(per 100,000 populations)

Age group	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44
Male	507	213	190	220	234	259	287	331	425
Female	415	170	163	168	262	403	420	323	297
Age group	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–	
Male	519	725	1,050	1,546	2,210	3,035	4,162	7,338	
Female	376	523	688	983	1,503	2,343	3,985	9,418	

Table 3 Regions and prefectures (according to MHLW)

Region	Constituent prefectures
Hokkaido	Hokkaido
Tohoku	Aomori, Iwate, Miyagi, Akita, Yamagata, Fukushima
Kanto	Ibaragi, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Yamanashi, Nagano
Hokuriku	Toyama, Ishikawa, Fukui
Tokai	Gifu, Shizuoka, Aichi, Mie
Kinki	Shiga, Kyoto, Osaka, Hyogo, Nara, Wakayama
Chugoku	Tottori, Shimane, Okayama, Hiroshima, Yamaguchi
Shikoku	Tokushima, Kagawa, Ehime, Kochi
Kyushu	Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, Okinawa

The number of general beds as defined by the above formula does not reflect needs for the number of pediatric beds in the community, since (1) the population of children (under 15 years of age) is as small as 14% of the total population, and (2) hospitalization rates among children are significantly lower than that among adults (Table 2). We, therefore, propose that the needs of beds for children and adults be calculated separately.

Goal and future perspectives of the health care system

The 1998 Medical Care Plan Development Guidelines contain the following directions: (1) sharing and coordination among various institutions, (2) setting goals of attainment in the medical resources, (3) securing emergency medical services, (4) securing medical services in remote areas, (5) securing health care professionals including physicians, dentists, pharmacists, nurses, etc., (6) securing other resources, (7) setting long-term goals and short-term plans. Item (3) "securing emergency medical services" was the first to refer to the organization of pediatric emergency medical services. The following is a quotation from the text.

"With respect to pediatric emergency care, in particular on holidays and at night, it is desirable that local authorities develop and describe a system of initial, secondary, and tertiary emergency care services meeting the actual needs of the area in consideration of changes in the climate of pediatric health care. If the available pediatric resources are limited in a secondary care area, local authorities may develop and describe a system for pediatric emergency services involving a few secondary care areas. In addition, local authorities are advised to promote accident prevention and maternal and child health, and to better inform parents and residents of pediatric emergency services available in the community through various information network channels."

This is another example of a structural flaw of the National Strategic Plan for Medi-

cal Care in that a pediatric emergency system (specific) is addressed without the whole pediatric health care system (general) being addressed.

Other issues

The National Strategic Plan for Medical Care consists of four major domains of medical services, general medicine, psychiatric medicine, infectious diseases, and tuberculosis. There were reasons for focusing on the four domains when the Law was established in 1948. The Plan was primarily concerned with inpatient care and its facilities, and the initial goal was to construct a sufficient number of hospitals and related institutions throughout the country. Since various infectious diseases including tuberculosis was prevailing then as leading causes of mortality and morbidity, the notion that the whole society be protected by keeping those who were affected within an isolation ward or a sanatorium was well accepted. The resultant scheme was a general hospital for general medicine, a mental hospital for psychiatric medicine, an isolation ward for infectious diseases, and a sanatorium for tuberculosis.

This scheme, however, does not adequately address maternal and child health, and the inequality of access to medical services between adults and children has been left unsolved because of marginal child welfare advocates.

Discussion

As overviewed above, the current national master plan for health care has been drafted with very little, if any, consideration of maternal and child health. It is apparent that under the current Medical Care Act and National Strategic Plan for Medical Care, adults and elderly take precedence over children and adolescents as beneficiaries of the Plan. Thus, we propose that under the new Medical Care Act, adults and children should be treated equally. The Law has favored

adults perhaps unintentionally but the claims of adults and children must now be given equal weight and the principle be clearly documented in the text. Such a decisive governmental commitment would create better quality health care services specifically designed for mothers and children. We also propose that the four major domains of medical care services be women of reproductive age, children, adults, and elderly rather than general medicine, psychiatric medicine, infectious disease, and tuberculosis.

Several issues merit further discussion. First of all, the organization of health care into primary, secondary, and tertiary levels needs to be assessed critically in relation to the needs of mothers and children. The three-tier structure in our system does not correspond to unique patient and family needs that are age and gender specific. Recent national disputes on pediatric emergency services are such an example. Many community emergency centers in the secondary care areas are staffed only by physicians and surgeons who are untrained in pediatric emergency medicine and equipped for basic adult inpatient services. We estimate that at least half of the secondary care areas are unable to provide either obstetric or pediatric emergency services on a 24-hour basis. Further, the vast majority of general hospitals in each secondary care area does not have pediatric wards, as studied in Gunma Prefecture by the present authors. Children have to be admitted to a mixed services ward with so-called swing beds. There is also no single child mental health unit available providing inpatient or emergency psychiatric services throughout Gunma Prefecture.

We need to recognize that care is not organized into distinct levels corresponding to specific functions, roles, administrative units, and population bases in many regions of Japan. Japanese patients are able to self-refer themselves and enter directly the medical care system at any level. Rather than having a primary care physician to first evaluate the problems, the Japanese patients often are seen directly by specialist physicians of any kind. In other words, Japanese physicians have less clearly defined roles than physicians in the UK.

To design and implement organized health care system that functions in practice, the role of the primary care physician has to be clearly defined and more importantly the defined role has to be agreed upon by all social sectors including MHLW and Japan Medical Association. In our view, a primary care physician is expected to play a more

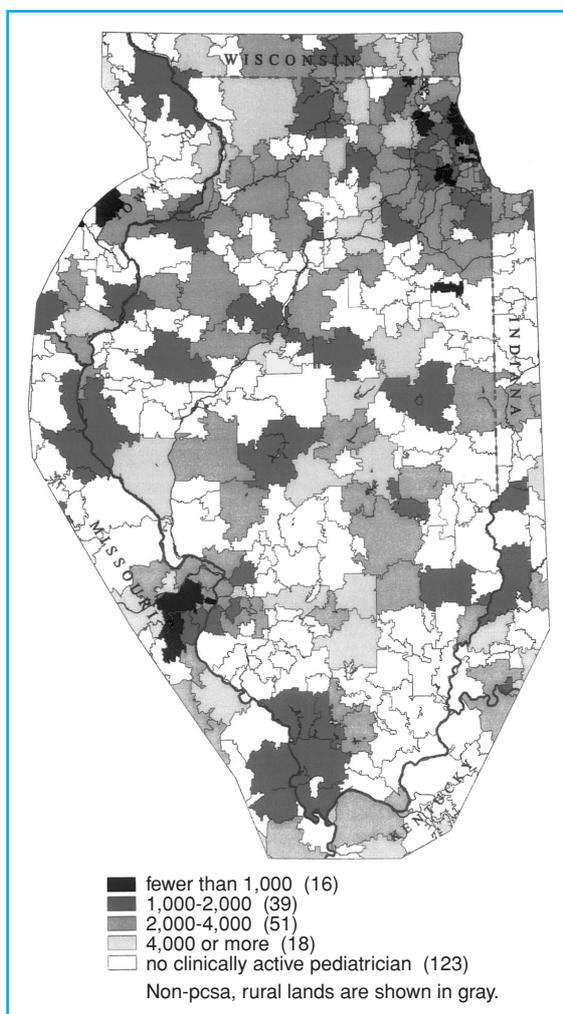


Fig. 1 Primary care service areas in the state of Illinois
 Primary care service area is a type of geographic area for health care. The map shows the number of children under 18 years of age per clinically active pediatricians in each primary care service area. (Reproduced with permission of David Goodman, The author of the original report)

complex role than used to, in providing comprehensive and coordinated health care services to the whole family rather than adult members of the family. The role of such a primary care physician includes pediatric acute care services and mental health counseling. To broaden the role of a primary care physician in practice is obviously not a simple task, although most Japanese people have health care needs at the primary care level. An agreement between Japan Medical Association representing health care providers and MHLW representing the national government is mandatory for initiating a fruitful discussion on the Medical Care Act amendment.

Secondly, we have to recognize that there is not enough informative data to address maternal and child health. For example, there is no validated data regarding current supply and practice of pediatricians: 1) How many pediatricians are there? 2) How are they distributed in each primary, secondary, and tertiary care area? 3) What work do they do? 4) What general practitioners do the same work? MHLW has been conducting annually the National Census of Physicians, Dentists, and Pharmacists, but “pediatricians”, “patient care physicians”, and “active physicians” and various other key terms are not adequately defined. Data on health care personnel and relevant facilities and services collected by MHLW are similarly flawed in terms of valid data collection, and not usable for obstetric or pediatric health services evaluation.

To our knowledge, there is no single

researcher in Japan specializing in the study of health care policy for children. This is in contrast to the large number of researchers specializing in the study of health policy for the elderly. Given the lack of interest in maternal and child health care policy, our laws and MHLW health policy do not adequately address for rapidly changing health care needs of children and families. We hope that MHLW take positive action to create a comprehensive database on maternal and child health to support the research activity of the field and its decision-making in maternal and child health.

In summary, there are three major problems that share a common background in making the reform of the Japanese maternal and child care difficult. First and foremost, the Japanese National Strategic Plan for Medical Care has not addressed maternal and child health care, although several specific pediatric topics have been covered. Second, there is no comprehensive data collection to support any policy development in maternal and child health. Third, there is a general lack of capability for policy development in public and private sectors. We hope that the present study provides a first step for drafting a big picture of maternal and child health for the future generation.

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Severe Acute Respiratory Syndrome (SARS)

—Summary of SARS outbreak, response in Japan, and actions at Infectious Disease Surveillance Center, National Institute of Infectious Diseases—

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Abstract

March 12, 2003, the WHO issued a Global Alert on the atypical pneumonia of unknown cause that broke out in Asia, naming the disease SARS. Supported by the cooperation of specialists from various countries, the WHO announced on April 15 that the pathogen was a new-type of coronavirus and proposed calling it SARS Coronavirus. Following international efforts, the WHO declared on July 5 that there was no new transmission of SARS. The outbreak came to an end, recording about 8,000 cases including about 800 deaths. Japan actively participated in the collection and sharing of information, establishment of testing and reporting systems in the country, and contributed to WHO and affected areas to control SARS. While 68 cases, including 52 suspect and 16 probable cases, were reported from the front line in Japan, all met the exclusion criteria and the number reported to the WHO was zero by the Government.

Although no new cases of SARS have since been reported, we cannot categorically state that this disease and the virus has been eradicated. We need to maintain the system for intensive surveillance and be prepared for a possible resurgence of SARS.

Key words SARS, Japan, Emerging infectious disease, Epidemic

Introduction

Following the global alert on SARS from World Health Organization (WHO) in March 2003, many countries cooperated under the initiative of WHO to identify the cause of this disease and enforce an appropriate response, and the outbreak gradually faded. On July 5, 2003, WHO announced that no country remained on the list of “recent local transmission.” As of September 26, SARS had affected 8,098 patients and

caused 774 deaths. While further cases were confirmed later, including 1 case each in Singapore and Taiwan, 4 cases in Guangdong Province in China, and 9 cases each in Beijing and Anhui Province in China, no new patients in the world have been confirmed since May 2004.

Although nobody has developed SARS for over 1 year now, this disease may not be extinct. We need to maintain the strengthened surveillance in case the disease reappears.

This article summarizes the SARS out-

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break, the response to SARS in Japan, and the actions taken by the authors and colleagues at the Infectious Disease Surveillance Center (IDSC), National Institute of Infectious Diseases (NIID).

First Cases of SARS

From November 2002, many cases of atypical pneumonia were reported in Guangdong Province, China, and WHO was aware of this accumulation of cases. As this situation became evident in 2003, ProMED and other information sources started to list this information in February. On February 11, 2003, WHO announced on its website that 300 cases, including 5 fatal cases, of acute respiratory syndrome had occurred in Guangdong Province, China, and efforts were being made to identify the pathogen. The Chinese government initially announced that these patients were affected by Chlamydia infection.

On February 19, 2003, avian influenza virus H5N1 was isolated from a father and his son, who had returned from Fujian Province near Guangdong to Hong Kong. The father died and the 9-year-old son recovered. This was the first case of isolation of H5N1 from humans after the 1997 outbreak in Hong Kong. Influenza experts all over the world noted this as a possible premonition of an influenza pandemic originating from Guangdong Province.

More news suggesting a pandemic of new-type influenza followed. One was the nosocomial outbreak of atypical pneumonia in Hanoi, Vietnam on March 5. Another was the occurrence of multiple nosocomial cases of atypical pneumonia in Hong Kong. Although the involvement of new-type influenza was suspected initially, investigation disproved that H5N1 infection was the cause. Various known pathogens were also disproved as the cause one after another, and WHO started a full investigation of atypical pneumonia of unknown origin among medical workers in Asia. As similar

pneumonia of unknown cause appeared in Canada, Germany, Singapore, etc. among the persons who visited Hong Kong, WHO recognized the situation as an outbreak of an unknown respiratory disease with the threat of becoming a worldwide epidemic. WHO named it “severe acute respiratory syndrome” (SARS), and issued a global alert (specifying an infectious disease of unknown cause requiring surveillance on a global scale). Later, outbreaks were reported in Beijing, Hong Kong, Taiwan, Singapore, Toronto, etc.

Spread of SARS: (1) A Common Factor among Cases in Hong Kong, Vietnam, Singapore, and Canada

The first patient in Hong Kong, who was considered to have initiated nosocomial infection, was a physician who reportedly had examined a pneumonia patient in Guangdong Province, China. He developed symptoms while staying at Hotel M (9th floor) in Hong Kong, was hospitalized in Hong Kong as having pneumonia, and died. Subsequently, many nosocomial cases of pneumonia occurred in this hospital. The Chinese American who was hospitalized as having pneumonia in Hanoi, Vietnam, and started nosocomial infection in Hanoi was found to have stayed at Hotel M (9th floor) at the same time as the first patient in Hong Kong. Similarly, the 10 persons who developed symptoms in Singapore, Canada, the U.S., etc. were also staying at Hotel M at the same time. These patients were staying in different guest rooms on the same floor (9th). While some form of direct or indirect contact among them was suspected, there was no evidence of such contact. None of the hotel workers developed symptoms.

No cases of large-scale spread of infection mediated by hotel stay have been reported after the outbreak centered on Hotel M. The spread of infection in this form is considered exceptional.

Spread of SARS: (2) Expansion from Nosocomial Infection to Communities in Hong Kong

The outbreak in Hong Kong was important, as it suggested the possibility of infection and epidemics in communities, in addition to the nosocomial infection that also occurred in Vietnam. SARS developed in 321 persons (as of April 15, 2003) among the approximately 15,000 inhabitants of an apartment house complex (A Garden). The investigation revealed the following facts: Of the several buildings in this complex, the cases were initially accumulated in Block E. The index case was a 33-year-old male who visited his relative in the hospital and a relative living in this building as well. This patient was associated with the infection in 2 relatives and 2 nurses living in A Garden, and the Hong Kong government considers that he initiated the outbreak. This male patient showed diarrhea as a symptom of SARS (while diarrhea was initially considered rare in SARS, it was found that some cases present with diarrhea). The rapid spread of infection among the apartment inhabitants was believed to be related to the lack of U traps in bathroom drains, the amplifying effect of bathroom exhaust fans, cracked sewer plumbing in Block E, aerodynamic effect in the lightwell to which bathroom windows opened, and other factors contributing to the spread of the virus. Although SARS is a respiratory infection, later study clarified that patient's stools frequently contain a large amount of virus. While this outbreak alerted us about the expansion from nosocomial infection to communities, there have been no further outbreaks in general residential districts in this pattern. The source and route of the spread of infection in this case are considered to be uncommon, like those in the outbreak at Hotel M. The investigation did not yield epidemiological or experimental evidence supporting the transmission of the

SARS virus via air, water, or infectious dust aerosol. In addition, no patients were reported in facilities around the apartment house complex, including schools, department stores, and movie theaters.

Registration of SARS Patients (Syndromic Surveillance)

Patient registration of infectious diseases is made usually after a definitive diagnosis has been fixed. However, in the case of the outbreak of a disease whose cause is unknown or difficult to identify, the traditional surveillance system based on the diagnosis of the disease may not be effective in achieving the needed sensitive monitoring of occurrence, as the process of diagnosing the name of the disease may slow the detection of the outbreak and delay response. An alternative is syndromic surveillance based on the reporting of a symptom complex before definitive diagnosis. This system is useful when an unknown disease or even a known disease requires speedy execution of epidemiological survey.

In the case of SARS, WHO for the first time promoted syndromic surveillance on a global scale, as it was necessary to collect epidemiological data concerning the number, location, and trends of patients. While an advantage of syndromic surveillance is the speedy understanding of the situation of outbreak, inclusion of other diseases showing similar symptoms is likely to occur without confirmation of pathogenic diagnosis. This could turn all the efforts into simple execution of surveillance for pneumonia. Therefore, it is necessary to introduce a method for screening (definitive diagnosis) as soon as possible. While SARS was initially defined as a symptom complex, virological assay results were added as supporting data to the case reports after SARS coronavirus was identified as the pathogen.

In brief, the disease concept called SARS was first highlighted by elimination of other possibilities, and measures and response

were based on the scrutiny of this concept. The role of the syndromic surveillance was considerable with respect to the speed of action. However, there is the possibility that “pneumonia syndrome” other than the “definite cases” of SARS might be included on one hand, and the possibility that SARS coronavirus infections failing to meet the case definition of SARS might be excluded on the other, hampering the accurate understanding of SARS. To gain better understanding, we need to examine both the confirmed cases with virological “proof” and the cases of SARS infection including non-typical cases.

Infectious Disease Surveillance Center (IDSC), National Institute of Infectious Diseases (NIID), Tokyo, Japan, has already executed such study on the occasions of the G8 summit on a small scale and then World Cup Soccer 2002, and this experience greatly helped the introduction of syndromic surveillance for SARS.

Discovery of the Causative Virus: SARS Coronavirus

Because of the concern regarding the reappearance of avian influenza from human subject or the emergence of a new influenza type, the problem of SARS was first addressed by the Influenza Network connecting WHO Influenza Collaborating Center (including the Department of Virology III, NIID) and influenza research centers in various countries. However, the involvement of influenza was disproved. Following the coordination by WHO, the SARS Network was formed by 11 research facilities in 9 countries (including Japan) participating in the Influenza Network. As the result of cooperative efforts with information sharing, a new type of coronavirus was identified as the pathogen of SARS, and WHO announced it under the name of SARS-CoV (SARS corona virus) on April 15, 2003. There had been no precedents of such an international cooperation of researchers aiming at the discovery of a

pathogen. The identification of the causative virus enabled pathogenic diagnosis, and the medical understanding of SARS progressed quickly. However, our knowledge remains at the investigational stage with respect to how the new virus gained the ability to infect humans, the pathology, causal treatment, and the methods of prophylaxis including vaccines.

Present Situation of SARS: World

The accumulated number of probable cases reported from all over the world to WHO and the situation updates are exhibited on the WHO website (<http://www.WHO.int/en/>), and the Japanese translation of this information is presented on the IDSC/NIID website. The focuses of epidemics were mainland China, Taiwan, Hong Kong, Vietnam, and Canada.

As a result of the international efforts to identify the cause and enforce an appropriate response, SARS gradually faded, and WHO announced that no country remained on the list of “recent local transmission” on July 5, 2003. As of September 26, SARS had affected 8,098 patients and caused 774 deaths. One patient in Singapore in September 2003 and 1 in Taiwan in December 2003 were reported as cases of infection within laboratories, and these cases did not cause secondary infection. These cases suggest that a high risk of infection is present in laboratories handling pathogenic organisms and such infection, if overlooked, can lead to the spread of SARS.

In addition, 4 cases of natural infection were confirmed in Guangdong Province, China in December 2003. Although these were sporadic cases of infection and not likely to cause the spread of infection, they suggest the need for continued surveillance for this disease.

The Ministry of Health of China further reported 9 cases of SARS in April 2004. One patient died and another developed into a serious condition requiring respirator treatment. The first patient, who had been study-

ing viruses at the National Institute of Virology, traveled between Beijing and his hometown in Anhui Province. The infection spread among the family, caregivers, and other people around this postgraduate student. The Ministry of Health of China admitted that the outbreak started from infection in the laboratory and attributed the cause to inappropriate biosafety management in the laboratory, non-compliance to rules, inappropriate performance of experiment procedures, and insufficient safety measures in the laboratory. This example emphasizes the need for strict enforcement of necessary infection control measures in performing experiments using SARS-CoV.

Response of the Japanese Government (Ministry of Health, Labour and Welfare)

On March 12, 2003, the Ministry of Health, Labour and Welfare (MHLW) issued a notice concerning the outbreak of pneumonia of unknown cause in Hanoi and Hong Kong for the purpose of ensuring information to relevant organizations. On March 14, in response to and in accordance with the WHO case definition of SARS, the Ministry stipulated the case definition for registration purpose and started the SARS surveillance in Japan. At the same time, MHLW developed and publicized measures for providing medical services, standards for patient management in hospitals and standards for controlling nosocomial infection. Other measures were also taken, including information disclosure, advice on travel to confirmed SARS-affected areas, reinforcement of quarantine, and a telephone service for the general public. On March 15, IDSC of NIID published "Urgent Information: Severe Acute Respiratory Syndrome (SARS)" on the IDSC website (<http://idsc.nih.go.jp/index-j.html>) to provide the information concerning SARS.

With respect to the positioning of SARS under the Law Concerning the Prevention of

Infectious Disease and the Medical Care for Patients with Infectious Disease (Infectious Disease Law), it was decided on April 3 that SARS should be handled as a "new category of infectious disease", so that administrative agencies could address SARS based on the Law. A government ordinance on July 14 added SARS to the list of specified infectious diseases. In August 2003, the Section of Infectious Diseases, Health Science Council submitted a proposal to designate SARS as a class 1 infectious disease in the Infectious Disease Law, and this designation was enacted by the amendment of the Law in November.

Projects conducted as urgent international assistance included surveys in Vietnam, Hong Kong, China, the Philippines, WHO Western Pacific Regional Office, etc.; dispatch of specialists for preventing the spread of infection; and provision of resources for nosocomial infection control to various countries.

Situation of SARS in Japan

After the launch of the SARS surveillance in Japan, the number of case reports from hospitals peaked in the earlier half of April 2003. The total number of reported cases was 68 (52 suspect cases and 16 probable cases). Except for the 2 cases exposed to close contact with suspect and probable cases respectively in Japan, all others were the suspected cases exposed with SARS overseas. The destinations of the travel of these patients were Taiwan, Hong Kong, mainland China (mostly Guangdong Province), and Singapore in decreasing order of frequency. Male cases were 3.0 times as many as females. The age of patients was 30–39 (25%), 20–29 (19%), 40–49 (18%), and less than 10 (16%). The Special Committee on SARS, formed under MHLW, reviewed all reported cases including the information on later clinical courses, and all cases were found to meet the exclusion criteria: "1. An alternative diagnosis can fully explain the illness. 2. Symp-

toms are improved by standard therapies such as antibiotic therapy within 3 days (high probability of bacterial infection or other antibiotic-sensitive disease). Based on this result, the probable cases reported to WHO were reclassified as not having SARS. The number of SARS cases occurring in Japan was amended to zero.

One traveler who visited Japan from overseas in June 2003 and developed symptoms was hospitalized and diagnosed as having SARS after returning to their home country. This patient was not diagnosed in Japan, and was not included in the report from Japan. At the time, case tracing surveys on persons having close contact with the patient were conducted with the cooperation of relevant local governments, MHLW, and IDSC, but no secondary infection in Japan was detected.

As the assay for SARS-CoV became available, a system for virological diagnosis was established in Japan. Tissue culture cells for the separation of SARS-CoV were supplied to Prefectural and Municipal Public Health Institutes in April 2003, as well as the positive control cDNA for RT-PCR in May, enabling assays at these institutions and Virology III/NIID. While 158 specimens were assayed at NIID, there were no positive cases. In fact, there have been no cases of SARS-CoV infection presenting with the symptoms of SARS in Japan. However, there are problems from the standpoint of virological diagnosis, such as that not all cases were tested by pathogenic assay, few paired sera have been submitted, and the time course of serum antibodies has been confirmed only in a limited number of cases.

Actions at Infectious Disease Surveillance Center (IDSC)

IDSC has been at anytime sharing information with WHO, U.S. Centers for Disease Control and Prevention (CDC), U.K. Public Health Laboratory Service (PHLS), and other international and national organiza-

tions engaged in infection control in collecting, evaluating, and publicizing official and unofficial information concerning infections in the world. IDSC has also been contributing to international infection prevention efforts as a partner of WHO's Global Outbreak Alert and Response Network (GOARN). Since the response to SARS emerged as an international issue from the beginning, the response at IDSC was commenced as a continuation of these routine activities. When the situation grew to require the entire workforce of IDSC, the SARS Response Team including Field Epidemiology Training Program (FET) was organized to address the issue.

1) International information collection and publicity in Japan

Working in close cooperation with WHO, NIID vigilantly watched the development of the situation following the outbreak of atypical pneumonia in China in November 2002, collecting information and strengthening cooperation. NIID increased alert when A/H5N1 influenza virus was detected on February 19 in Hong Kong from the patients with influenza-like symptoms, 3 members of a family returning from the travel to Fujian Province. The outbreak of respiratory syndrome among medical workers in Hanoi, Vietnam on March 5, followed by the report of a similar situation in Hong Kong on March 7, and the issuance of the WHO's Global Alert concerning the outbreak of respiratory syndrome of unknown cause prompted the preparatory work for providing information to Japanese citizens. As WHO issued a worldwide Travel Advice on March 15, NIID in cooperation with MHLW started to publish the "Urgent Information: Severe Acute Respiratory Syndrome (SARS)" page on the IDSC website in the next week. This page included the translation of the official announcements of WHO, with additional explanation as needed. Updating was continued every day from the WHO's first update on March 17

to the “Update 96” on July 7. Updating is continuing to reflect the latest bulletins.

The official information from WHO, as well as the information obtained through the communication with the above-mentioned GOARN and various countries, was supplied to relevant organizations, and compiled into technical information materials for measures in Japan. These were used at seminars and training courses for SARS held by MHLW, and also were supplied for use in seminars and training courses for SARS held by the attendants of the central seminars.

2) Technical assistance for measures in Japan

The patient surveillance in Japan started with the notification of MHLW on March 16 requesting case reporting based on WHO’s case definition. Because the cause of SARS was unknown, symptoms were too nonspecific to support clinical diagnosis, and no method for early diagnosis was available at that time, syndromic surveillance was conducted based on the case definition using clinical symptoms, findings, and epidemiological linkage. While such surveillance was likely to cause inclusion of many patients with diseases other than SARS showing similar symptoms, adequate preventive measures against infection had to be practiced for the patients with SARS. Because this situation could cause difficulty in making judgment in clinical practice, IDSC set up a system to answer questions from hospitals and health departments of local governments. Questions via telephone and e-mail were answered, and answers to frequently asked questions were posted on the IDSC website. While WHO was frequently announcing guidelines on patient management, hospital discharge, etc., which were practically regarded as international standards, IDSC developed Japan’s own guidelines to supplement them in the management of ambiguous cases. These covered various topics from basic patient management and response in outpatient clinics to the selection of disinfectants

and disinfection methods for workplaces and homes. After the new coronavirus was identified as the pathogen of SARS and the virological tests for SARS-CoV became available in Japan, IDSC in cooperation with Department of Virology III had to manage the numerous requests for testing. IDSC worked as the secretariat coordinating the roles of local governments and Department of Virology III. In connection with this response, guidelines for SARS-CoV tests and those for laboratory biosafety were also announced. The information from IDSC reflected the frequent updates and incorporated the responses and guidelines in the U.S., Canada, Singapore, and other countries.

As the surveillance in Japan became established and suspected and probable cases of SARS reported from local governments to MHLW and the information in the reports of suspected and probable SARS cases from local governments to MHLW started flowing from the Ministry to IDSC, the data were converted to electronic form, linked to assay information and compiled in a database of patients who might have SARS in Japan.

In the incident where a traveler from a SARS affected area developed SARS and traveled to Japan, we provided technical support to the Operation Center established in MHLW, prepared an on-site epidemiological survey manual, and sent active surveillance team including FETP, to support epidemiological surveys in response to the request from relevant

3) Technical assistance for international measures

Personnel have been sent on a long-term basis from IDSC to Communicable Disease Surveillance and Response (CSR; the organization responding to the SARS outbreak) in the WHO headquarters. This arrangement has proved very useful in the response to this kind of situation. The epidemics of SARS were centered on Asia and in the jurisdiction of the Western Pacific Region Office (WPRO)

among the regional offices of WHO. IDSC sent 5 personnel to Hong Kong and Manila in response to the request from GOARN or WPRO. They supported epidemiological surveys and nosocomial infection control measures in Hong Kong and worked in Manila to support data analysis and the development of guidelines for the areas covered by WPRO. Various kinds of information were obtained through such cooperation and then utilized for the response in Japan.

Infection Routes, Symptoms, and Infectivity of SARS: Summary of Epidemiological Surveys

At present, the SARS virus is believed to infect mostly from human to human. Based on the situation of reported infection, the highest risk of infection is associated with “close contact with SARS patients,” such as giving nursing care or assistive care to SARS patients presenting with pneumonia (especially in severe cases), living with patients with symptoms, and direct contact with the body fluid or airway secretion of patients. Droplet infection and contact infection via airway secretion are considered the most important route of infection. The possibility of fecal-oral infection, airborne infection, etc. cannot be ruled out, but these are considered rare. SARS initially spread from Hotel M in Hong Kong, but there has been no further incidence of infection spread mediated by hotels. The spread of infection in general residential districts such as A Garden was also exceptional, and no similar outbreaks have been reported. While cases of secondary infection in aircrafts have been reported, all these cases were infection from passengers with manifest symptoms, and infection from asymptomatic carriers has not been reported. The epidemiological surveys conducted so far indicate that a large majority of patients became infected by secondary infection from medical workers and families of SARS patients. The most impor-

tant factors were the spread within medical institutions treating symptomatic patients and the leak from there to communities.

While 80 to 90% of SARS patients showing symptoms of pneumonia start to recover within about 1 week, 10 to 20% develop into a serious condition (acute respiratory distress syndrome: ARDS). Although there are geographical differences, the mortality rate is about 10% on average. Infectivity is stronger during the climax phase of pneumonia and in severer patients. Therefore, nosocomial infection control in hospitals treating such patients is particularly important. Although patients with fever and coughing in the prodromal phase have only weak infectivity, adequate precautions must be taken in the treatment of these patients. The possibility of infection from patients in the latent or asymptomatic phase is none or very low, if any. Therefore, the possibility of the spread of infection in community is very low. While each SARS patient is has the potential to transmit infection to 2 or 3 unprotected persons ($R_0=2-3$), a minority of patients might each transmit the infection to 10 to dozens of persons. Most of these patients, called super spreaders or hyper transmitters, developed severe conditions and died, and little is known about the factors (patient background, environment, use of protection against infection, etc.) associated with such patients. Multiple super spreaders developed symptoms and expanded the spread of infection before the presence of SARS was noticed in the outbreaks in Hong Kong, Taiwan, Singapore, and Toronto. On the other hand, it is estimated that Vietnam, the U.S., the Philippines, Korea, and Japan were fortunately visited by few or no super spreaders. The analysis of patient background indicated high mortality rate among aged persons, high incidence of infection and low mortality rate in the 20–49 age groups, and low incidence of infection and low mortality rate among children. No explanation has been given to account for these observations.

Prevention of the Spread of Infection

As the medical workers experiencing outbreaks invariably remark, the spread of nosocomial infection took place because nobody recognized the infectivity of this disease and treated it as ordinary pneumonia in the early stages of the SARS outbreak. In other words, this disease spread in hospitals taking advantage of the lack of "precautions against infection." The basics of nosocomial infection control are "the introduction of the concept of standard precautions" and "the orderly use of preventive measures." All medical institutions need to ensure the understanding of this concept and the preparedness to use it whenever needed. Aside from SARS, we now need to raise the standard of infection control in general. It is also necessary to ask for the cooperation of citizens seeking medical treatment (ask them to report any fever, cough, and recent overseas travel on the phone rather than at the time of visiting physician, ask them to use protective equipment such as a mask, etc.).

Fortunately, Japan has not experienced the spread of SARS infection, and no cases have occurred in Japan. However, there are no guarantees that this situation will continue into the future. We expect that the spread of SARS infection in Japan can be prevented fairly well by means of the triage of patients with infections in general, the introduction of standard precautions in general medical institutions, the introduction of barrier nursing in situations needing it, and the strict infection control of severe patients. In particular, general outpatient clinics seeing many cases of respiratory infections need to be prepared against emerging, probably rare diseases such as SARS, and this should be achieved through improving practice, such as the early triage of patients considered to have pneumonia (use of telephone consultation, history taking at the time of reception, flexibility in the order of patients examined, place of examination,

etc.), use of surgical masks by caregivers seeing patients with pneumonia, and asking patients to wear masks, considering the acceptance by the public.

The experimental use of SARS-CoV at the institutions engaged in virological study and testing is expected to increase. These institutions need to ensure appropriate installation and management of biosafety facilities, as well as ensuring full awareness of laboratory workers.

Conclusion

After the WHO Global Alert on SARS, worldwide efforts were made to identify the cause and enforce an appropriate response. The pathogenic organism was identified exceptionally quickly, and new information and knowledge on this disease are still being accumulated. The emergence of SARS highlighted many problems in the health care system, infection control, public health, and health administration. While improvements were achieved quickly in some aspects and belatedly in others, many problems remain unsolved. While response to a specific disease such as SARS is certainly important, the most important step in preventing the spread of infection is to raise the standard of measures against infections in general.

After being active from mid March 2003 to early July, the SARS Response Team in IDSC was dissolved for the time being on July 7. The response to SARS required the entire workforce of IDSC during a period of about 3 months, and services in other areas almost declined. The most important factor in crisis management is human resources. We need further efforts in staff training and strengthening organizational capabilities. (Thanks to the understanding and cooperation from various parties, the staff in IDSC was increased by the addition of 6 chief researchers in charge of SARS.)

The experience in the SARS outbreaks and the increase in the IDSC staff greatly helped the response to the avian influenza

epidemics that occurred in and out of Japan from 2004 to the present, as well as the assistance to local inhabitants in infection

control following the Sumatra Earthquake and Tsunami.

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Problems in Breast Cancer Screening

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Abstract

Breast cancer in Japan is increasing. The prevalence peaks in middle age (30 to 65 years old) and declines at higher ages. In contrast, breast cancer in Western countries occurs predominantly in old age. In Japan, breast cancer has already been ranked the highest among the causes of cancer deaths in females aged between 30 and 57. The prevalence of breast cancer in Japan, albeit increasing, is less than one-third of that in Western countries, but it represents a considerable problem, since the disease affects women in the most productive age. The Ministry of Health, Labor and Welfare of Japan considered that allowing the increases in the breast cancer prevalence rate and death rate to continue would be a discredit to the country, in view of the fact that the breast cancer death rate in Western countries has been decreasing rapidly since the 1990s and the prevalence rate has been approaching a plateau. In March 2000, the Ministry issued Notification No. 65 of the Health and Welfare Bureau for the Elderly, in which conventional breast cancer screening relying on inspection and palpation was to be bolstered by the biennial MMG screening of women aged 50 and older. In the spring of 2004, the lower age limit for MMG screening was lowered to 40, considering the peak of prevalence in middle age in Japan. However, a system for MMG screening cannot be established in a day by simply issuing a notification. What we need in the meantime are the combined efforts of the national government, local governments, industries, mass media, and medical circles to educate and raise awareness of breast cancer, which should enable accurate MMG screening networks to be successively activated. For the detection of breast cancer, we need to develop a naturally acceptable route in which all women, in cooperation with all family members, perform breast cancer palpation, obtain advice from friends, and visit medical services. Although Japan lags behind Western countries in breast cancer issues, the intellect of the Japanese people is sufficiently high to support this approach. A national project like this should be realized in the timescale of a decade.

Key words Breast cancer screening, MMG screening, Inspection and palpation, Self examination

Introduction

Articles featuring false-negative cases of breast cancer occurring in inspection-palpation screening and emphasizing the importance of mammography (MMG) screen-

ing appeared in the mass media in the fall of 2003, triggering lively discussion on MMG screening of breast cancer. Concerns had already been expressed regarding the screening depending on inspection and palpation without the use of MMG, and steady efforts had been made for improvement. There had

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also been envy over the achievements in Western countries, such as the development of the system for MMG screening since the 1990s, the high accuracy, and the insurance coverage of costs. A few attempts of MMG screening had also been reported in Japan.

However, for the physicians on the front-line conducting breast cancer screening using inspection and palpation with a combined sense of passion and despair, the plan to introduce MMG screening in a day seemed totally unrealistic. While MMG screening was regarded as a remote goal, inspection-palpation screening was continued on the premise that MMG screening was not easily attainable.

Steady efforts toward the realization of MMG screening in Japan have been made under the unspoken pressure of the fact that MMG screening was being used in every industrialized Western country and the death rate of breast cancer was decreasing in many.

To address this difficult challenge, the Ministry of Health, Labor and Welfare organized the Study Group on Cancer Screening and a draft plan for MMG screening was developed. The Accuracy Control Committee was subsequently established to ensure the accuracy of MMG as an organization formed around the core of the Japan Association of Breast Cancer Screening, the Japanese Breast Cancer Society, and the Japan Radiological Society. Based on these developments, the Ministry issued Guidelines for Health Education for Cancer Prevention and Implementation of Cancer Screening (Notification No. 65 of the Health and Welfare Bureau for the Elderly) dated March 31, 2000. The guidelines stated, "Women aged 50 and older should be examined by biennial inspection-palpation screening and mammography screening (oblique view in one direction) as a rule." The guidelines also stipulated the standards for the use of mammography equipment, as well as the standards for training and qualification of technologists and reading physicians.

However, these guidelines were not ad-

ministrative orders but recommendations. Although they declared the time had come to introduce MMG, only a few advanced medical institutions followed the recommendations.

While the progress toward MMG screening remained slow, everyone concerned was shocked by the report in the *Asahi Newspaper* that MMG screening was being used in only less than half of all breast cancer screening occasions. The shock came from their bewilderment, perplexity, and impatience.

The Study Group on Cancer Screening subsequently expanded the scope of activity. Considering the recent increase in breast cancer prevalence at ages 45 to 49, it was decided that the lower age limit for screening would be lowered from 50 to 40 years old, effective as of March 2004. The Committee's report to the Ministry included the following: (1) screening should cover women aged 40 years or older; (2) screening should be performed using both inspection-palpation and MMG; and (3) the subjects in their 40s should be examined by MMG in two directions, because the high density of mammary glands adversely affects accuracy. These recommendations were published as a supplement to Notification No. 65 of the Health and Welfare Bureau for the Elderly. Although these recommendations were logical and reasonable, they aggravated the perplexity and impatience both among medical professionals and among the general public.

In this article, I offer a personal opinion as to how we should deal with this situation, focusing on MMG screening of breast cancer in Japan.

How Breast Cancer Is Detected in Japan

Figure 1 shows the statistics of how breast cancer was detected (why patients consulted a doctor) in the patients undergoing surgical treatment at the Department of Breast Surgery, the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.¹ In an overwhelming majority of cases, the

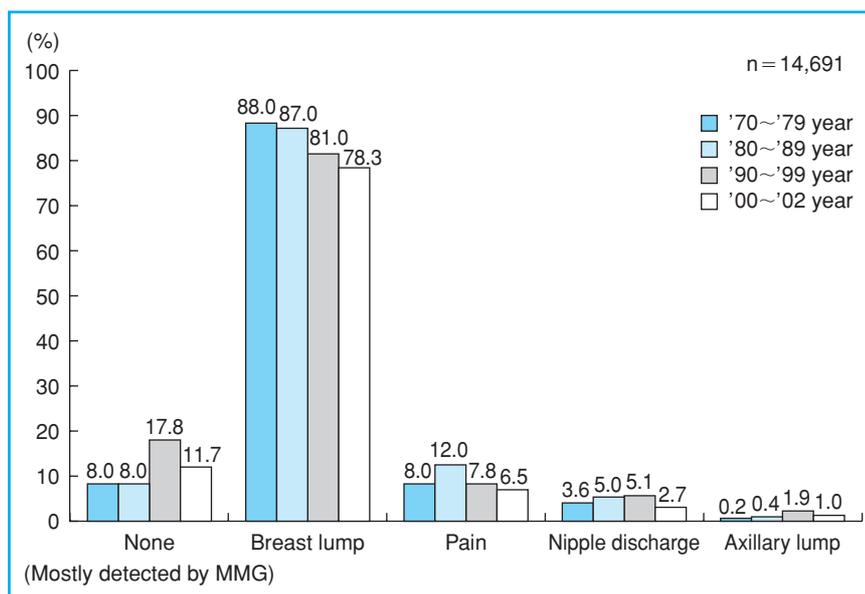


Fig. 1 Initial symptoms (Multiple answers)
(Department of Breast Oncology, the Cancer Institute Hospital of JFCR)

first symptom was a palpable lump (breast mass), which occurred in more than 80% of patients. After the presence of cancer was confirmed by various tests at the hospital, more than 90% of patients had palpable breast lumps. Cases detected by other means were extremely few. Women with palpable breast lumps should consult a doctor as a matter of course. They are symptomatic patients, who are not supposed to receive breast cancer screening. The cases of breast cancer detected by MMG screening or ultrasound screening in symptom-less women without breast lumps were as few as 11.7% in the years 2000–2002.

This fact clearly illustrates the incoherence of breast cancer screening in Japan. MMG screening is contributing little to the detection of breast cancer in Japanese women at present, and most of the detected cases are symptomatic patients with lumps. While women with lumps do not necessarily have cancer, most patients with breast cancer have lumps. Because many such patients are not aware of the disease, they do not consult a doctor immediately and receive inspection-palpation screening. This results

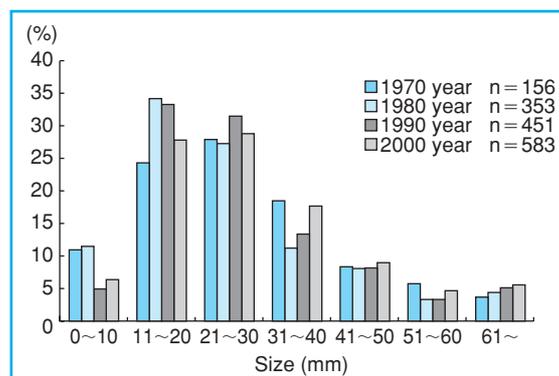


Fig. 2 Tumor size distribution at 1-cm intervals
(Department of Breast Oncology, the Cancer Institute Hospital of JFCR)

(Quoted from the Japan Society of Breast Health (ed.). Breast Care for Every Woman. Tokyo: Japan Medical Planning; 2004)

in a high detection rate of breast cancer in screening. However, considering the significance in reducing the mortality rate, detection of these cases does not contribute to the effectiveness of inspection-palpation screening.

Figure 2 shows the longest diameter of a tumor in the patients with palpable lumps at

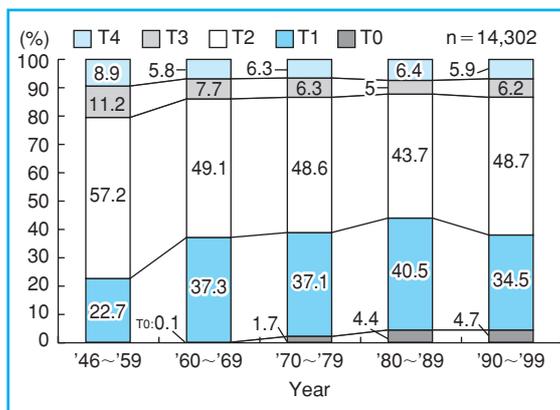


Fig. 3 Changes in T-staging

(Department of Breast Oncology, the Cancer Institute Hospital of JFCR)

the time of surgery.² The data for 1970, 1980, 1990, and 2000 do not reveal a consistent decreasing trend in tumor diameter, and the most frequent diameter remains in the range from 25 to 30 mm. T1 tumors (≤ 2.0 cm) represent 35 to 40%, and T2 tumors ($2.1 \leq T \leq 5.0$ cm) amount to nearly 50% (Fig. 3). As far as we see here, Japan is an underdeveloped country with respect to breast cancer.

Correlation between Palpation and MMG

Then, why is there a growing need for MMG screening of breast cancer now?

Figure 4 compares the ability of inspection-palpation and MMG to detect lumps. As mentioned above, the size of the lumps in the new patients visiting the Department of Breast Oncology of the Cancer Institute Hospital, Tokyo is 2.5 to 3.0 cm in average. Lumps with diameters from 2.0 cm (the size of a 1 yen coin) down to about 1.5 cm are palpable. In many cases, a lump that is as small as 1.5 cm feels like an indistinct core in fatty tissues. As the size approaches 1.0 cm, lumps become much less palpable. In contrast, MMG can detect smaller lumps as well as large palpable lumps. The mean diameter of non-palpable breast cancer (T_{np}; tumor not palpable) detected by MMG is about

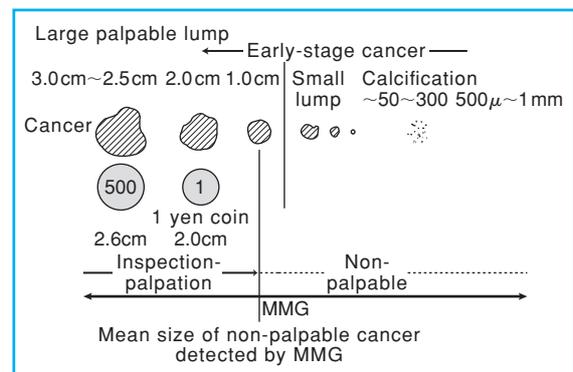


Fig. 4 Ability of inspection-palpation and MMG in lump detection

1.0 cm. Smaller lumps down to about 5 mm can be diagnosed as cancer. Even smaller tumors can be diagnosed in the case of daughter tumors near the main tumor, but diagnosis of a solitary tumor of this size is difficult.

On the other hand, there is a splendid method for diagnosing breast cancer, namely, the depiction of calcified lesions. Calcification in the mammary gland can be cancerous or benign. In both cases, it usually occurs within mammary ducts. Calcification in cancer is localized to the tumor site and segmentally confined to one lobe. The calcification has a characteristic irregular shape, the appearance of which resembles a beer bottle that has been smashed on the pavement, and mainly consists of calcium phosphate. Sizes are distributed in the ranges of about $50 \mu\text{m}$, about $500 \mu\text{m}$, about 1 mm, etc. The ability of MMG in discerning this calcification is unrivaled. In view of the capability for imaging small tumors and calcification, as well as the objectivity of photographic recording, we can clearly see the advantage of MMG over inspection-palpation.³

While MMG screening of breast cancer is definitely superior to inspection-palpation screening, it cannot detect all tumors. Clearly palpable masses are often missed by MMG. In many cases, masses are hidden in dense shadows of well-preserved mammary glands. False-negative cases, where masses are over-

Table 1 Guidelines for health education for cancer prevention and implementation of cancer screening (Notification No. 65 of the Health and Welfare Bureau for the Elderly)

March 31, 2000

- Women below 50 should be examined by annual inspection-palpation screening.
- Women aged 50 and older should be examined by biennial inspection-palpation screening and mammography screening as a rule.
- The reading of each mammogram should be performed by two physicians, one of whom should preferably be a physician who has completed a training course, such as the one conducted by the Accuracy Control Committee, and has sufficient experience.
- The mammography equipment should comply with the specifications defined by the Japan Radiological Society, and the operation of mammography should be performed preferably by a medical radiation technologist who has completed a training course, such as the one conducted by the Accuracy Control Committee.

looked due to reading errors, and false-positive cases arising from a fear of overlooking also occur frequently. Dependence on MMG may cause a problem of over-treatment. While clearly depicted masses do not involve this problem, tumors detected by microcalcification (such as those verified by the mammotome) can be treated excessively cautiously with unnecessary surgical treatment.

Although MMG screening has difficulties and detriments as mentioned above, it is the best method for breast cancer screening in Western countries, where breast cancer is much more prevalent than in Japan and women tend to have large breasts making palpation difficult. In Japan, too, MMG will clearly become the decisive means for breast cancer screening in the future.

The Japanese government is now encouraging MMG screening. The text of Notification No. 65 of the Health and Welfare Bureau for the Elderly (Table 1) imperatively states that MMG screening should be used as a rule. The supplement provided by the Study Group on Cancer Screening in March 2004 states the following:

- Traditionally, self-palpation has been re-

commended, because breast cancer is often detected by the patient's awareness of a lump (mass) and it is the only cancer that can be examined by the patients themselves. However, breast cancer with a palpable lump is already in an advanced stage with a high possibility of metastasis to other organs, and the failure to detect such cancer clinically should not be allowed to occur.

- It is necessary to ensure that cancer is detected in a stage presenting no subjective symptoms before a palpable lump develops.

The wording of the above recommendations seems to lack sympathy for the actual situation and grievances of clinical professionals.

Bewilderment of Clinical Professionals at MMG Screening Recommendations and the Mass Media Coverage Claiming MMG Screening Is the Only Effective Breast Cancer Screening

Although breast cancer is increasing rapidly in Japan and more and more new patients are being identified, there are only a limited number of hospitals specializing in breast cancer. Because of the escalating trend for patients to choose renowned hospitals, patients with breast cancer have to wait for more than a month or even two months before admission. This is a detrimental effect of the uniformization and indiscrimination in the health insurance system of Japan. This problem will not be solved unless appropriate measures are urgently taken, such as classifying the levels of hospitals, giving preferential treatment to breast cancer specialists and authorized medical institutions, and introducing relevant competition principles. It is the uniformity of the provision of medical services that is causing the overcrowding of the breast surgery departments of famous hospitals, much to the inconvenience of patients.

However, women wanting an examination

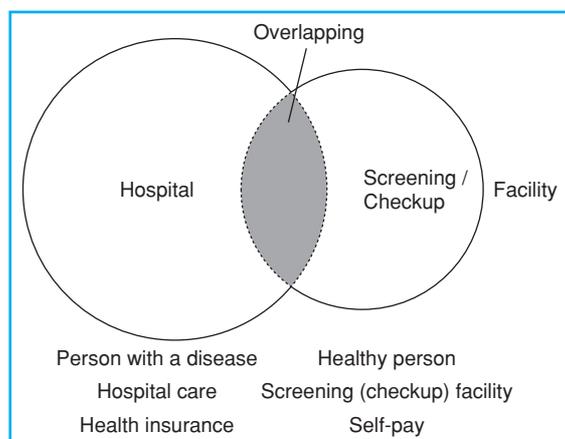


Fig. 5 Gray zone between medical care and screening (checkup)

visit the breast surgery departments of such hospitals because they offer examination resources of the world's highest levels. As a result, examinations for the purpose of screening drive away patients with breast cancer who are in urgent need of examination. While a small number of such cases may be acceptable, tens of such cases thwart the execution of the hospitals' mission. Women visiting hospitals with anxiety over breast cancer usually claim that they have trouble or pain in the breasts. They assert their rights without realizing that they are doing wrong. According to the rule, such persons must receive examination at medical checkup facilities, and the cost must be self-paid. This cost is usually less than 10,000 yen (US\$100), but it is much higher than the self-paid portion of the examination cost using health insurance, and hence many women choose to visit hospitals. While the mass media have been encouraging the violation of the law concerning mass screening in this form, the Ministry of Health, Labor and Welfare has not issued a statement against such media coverage. The deficit in the national health insurance system is bound to increase.

A hospital is a place for patients with known or strongly suspected diseases. On the other hand, persons without subjective symptoms who are anxious about health and

who want to confirm the absence of disease should receive screening or checkup.² While medical services for patients at hospitals are covered by medical insurance and patients can receive medical care at low cost, as stipulated in insurance policies, screening (checkup) is a different matter. It is outside the scope of the Health Insurance Law, and the cost must naturally be self-paid.

However, there is a gray zone between medical care and screening (checkup), where the two overlap each other and cannot be discriminated clearly (Fig. 5). From the physician's perspective, it can very roughly be said that an examination falls under medical care if there is a lump and screening (checkup) if there is none, because a palpable lump is the main sign of a breast tumor, whether benign or malignant. However, how do we classify a woman receiving an examination because she has pain, because something is wrong with a part of the breasts, or because her mother and sister had breast cancer? We cannot discriminate these cases and any methods of discrimination would cause problems. In fact, public facilities such as cancer screening centers offer examinations on a self-paid basis in principle, but users are told at the time of making a telephone appointment that part of the cost will be covered by insurance if they have some specific medical problems and the cost must be self-paid if they have none. Given this explanation, users would choose either of the two options if there were some difference in examination procedures. If there is no difference, users can pay less by stating that they feel that there is something wrong with their breasts. In this logic, cancer screening centers are no different from the outpatient departments of hospitals. However, the Ministry has not taken any action to correct this situation. This attitude is contrary to the policies to reduce deficits, such as to limit the medical services for people lacking major symptoms by raising the percentage of the self-pay portion from 20% to 30% and raising the follow-up consultation fee.

Every citizen should recognize that screening (checkup) with higher accuracy^{2,3} costs more and the maintenance of their own health requires investment. In making this investment, citizens should seriously evaluate the accuracy of screening. As discussed above, although the discrimination between medical care and screening (checkup) must be made, this discrimination is very difficult. People with no reason to suspect a disease should never try to save on the cost for screening (checkup) by receiving it in the form of medical care covered by medical insurance. As stated in the public brochures, if you know you have a lump in the breast, do not wait until municipalities offer free screening but see a doctor; you do not want to throw your health away. Every person should understand the need for paying properly defined charges to secure their own health.

Where to Look for Accurate Screening

At present, facilities performing MMG screening in Japan include the following:

- (1) Screening centers, cancer screening centers, etc. attached to hospitals (in separate buildings);
- (2) Public and semi-public facilities entrusted by local governments, such as screening centers, cancer screening (checkup) centers, Health Service Associations, and Public Health Service Associations;
- (3) Privately operated health screening facilities and screening centers operated by companies for their employees; and
- (4) Privately operated breast cancer screening clinics.

The facilities under (1), (2), and (3) are reasonably well equipped, but equipment renovation to replace aged units with the newest models is rarely possible. Difficulties also lie in the recruitment of specialist technologists and physicians, as well as the capability to double check mammograms. These facilities are inferior to hospitals in terms of

equipment, human resources, and accuracy, and upgrading these factors would require considerable investment of money and manpower. It seems that dumping is taking place among some of these facilities. Category (4) includes a small number of facilities offering self-pay screening services, where experienced physicians recognizing the value of MMG are providing highly accurate screening for a price. Facilities in this category are gradually increasing in number. While their services compare favorably with those of top-ranking hospitals, the shortage of human resources is a major problem.

As discussed above, the realization of MMG screening is not easy. The development of screening networks may not be completed in a short time, as there will be constraints in various aspects, such as location, fund, specialist technologists, specialist physicians, accuracy, proficiency, and experience. It will probably take 10 years.

Education and Raising Awareness about Breast Cancer

As discussed in the above sections, the announcement to start MMG screening alerted the nation to the urgency of need, and it exerted a strong impact in concert with the thrust from the mass media. Local governments and other relevant parties are now implicitly but inevitably forced to make further efforts to take long, difficult steps. Women and their family members are waiting in expectation.

However, from the perspective of front-line medical institutions, the present situation in Japan is far from the goal of promoting MMG screening.¹ Although the prevalence of breast cancer is much lower in Japan than in Western countries and the relatively small size of the breasts of Japanese women means easier examination as compared with Western women, nearly 50% of breast cancer cases in Japan are detected at stage II.

The most important areas in which Japan is lagging behind are education and raising

awareness about all aspects of breast cancer. The enviable fact that MMG screening has reached 70 to 80% in Western countries is supported not only by the development of MMG screening networks, but also by the breast cancer education and awareness efforts targeted at both women and men. Although the above-mentioned statistics show no progress in the early detection of breast cancer cases since 1970, my impression in practice at the Department of Breast Surgery, the Cancer Institute Hospital of JFCR suggests that breast cancer detected by screening has increased since the Asahi Newspaper coverage of breast cancer issues. The intellect of the Japanese people is sufficiently high to improve the underdeveloped situation regarding breast cancer. We should all take measures to educate and raise awareness so that we can create an environment in which women react without fear to breast cancer and all people seriously work toward the early detection.

To this end, it will be necessary to provide education in breast cancer in general, facts about the increase in breast cancer, practice of self-examination, basic knowledge of MMG, significance of receiving MMG, screening networks, etc. Physicians, hospitals, industries, mass media, local government, and the state should collaborate enthusiastically to repeat educational efforts concerning all aspects of breast cancer. Education and awareness projects will require much less funds as compared with the development of MMG screening networks, and the effect will be considerable, if conducted repeatedly. As I frequently leave the operating room and participate in various education and awareness activities, I feel that the effects of such activities are expanding year by year. The Susan G. Komen Breast Care Foundation, headquartered in Dallas, U.S., raises \$100 million every year from various enterprises through marathon events held for breast cancer campaigns at various locations throughout the world. Their scale, enthusiasm, and performance are astonishing. The

Foundation's efforts to fight breast cancer are gaining people's sympathy nationwide, and we cannot help but applaud them.

As education and awareness activities are continued in Japan, women will be more cautious about breast cancer, self-examination will be practiced widely, and the size of breast cancer at the time of detection will diminish. Meanwhile, MMG screening networks will be developed step by step, and hopefully we will be able to respond to the recommendation of the Study Group on Cancer Screening. This is the rough road map that should be presented before the announcement of MMG screening.

Personal Opinion on the Development of MMG Screening in Japan

1. The above discussion should provide a glimpse of the direction of the development of the MMG screening network in the future. The proposals of the Study Group on Cancer Screening⁴ contained the following remarks concerning the development of the system for implementation of the screening:

- Prompt introduction of MMG screening should be planned.
- The state, prefectures, municipalities, and related organizations should cooperatively take necessary measures so that screening can be provided in all municipalities starting from fiscal 2005.
- The state, prefectures, municipalities, and related organizations should cooperate in developing training courses for radiation technologists and physicians performing screening, recruiting human resources, and ensuring sufficient accuracy control.
- It is also important to ensure accuracy at medical institutions that perform detailed examination after screening.

The Ministry of Health, Labor and Welfare issued the Health and Medical Service Law for the Aged based on these proposals. From the text of the Law, we can expect that screening (checkup) conducted by local governments will naturally be subsidized

from the national budget. In fact, when Ms. Yoriko Madoka, Member of the House of Councilors, asked about the measures for improving MMG screening before the House of Councilors Standing Committee on Audit in the presence of the Prime Minister, her question was answered by Mr. Sakaguchi, Minister of Health, Labor and Welfare, as follows: Buying MMG equipment is no easy matter because it costs as much as 20 million yen US\$0.2 million per unit, but it is a means to save human life. Therefore, the government is attempting to promote the use of MMG across Japan while reducing the lower age limit for screening from 50 to 40. His answer implicitly suggests future subsidizing from the national budget.

2. Semi-public screening facilities are unable to perform highly accurate screening as long as they are being operated separately from each other. We should seek a means to promote cooperation and unification among them.

3. Self-paid MMG screening provided by private physicians may be improved further,

if a larger number of experienced physicians come to operate such screening facilities and work in friendly rivalry. The general public should make efforts to entrust their own health to better medical services and actively evaluate the quality of screening to improve accuracy.

4. The facilities providing the most accurate MMG examination in Japan are top-level hospitals that are performing breast cancer surgery in clinical practice. Using these facilities may be the fastest way to success. This will require several conditions. In the U.S., such examination is covered by Medicare, Medicaid, and insurance policies for wealthy people. In Japan, cancer centers and specialized hospitals should be devoted to treatment, and some other hospitals, as long as they have reserve capacity, should cover MMG screening that is recommended under health insurance.

While items 1 and 4 above require discussion and decision at the National Diet, these seem to be the most feasible solutions.

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Activities of the Japan Medical Association in the Fight against Infectious Diseases

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Abstract

The Japan Medical Association has set up the Risk Management Task Force on Infectious Diseases to help counter infectious diseases. The Infectious Diseases Risk Management Committee, which includes experts in infectious diseases, and the Infectious Diseases Risk Management Conference, consisting of representatives of prefectural medical associations from throughout the country, were organized to discuss issues related to infectious diseases, including measures against severe acute respiratory syndrome (SARS) and measures against large-scale infectious diseases.

Specific activities aimed at providing information on infectious diseases include publication of guidelines for the diagnosis and treatment of infectious diseases for physicians, under the supervision of JMA and the Ministry of Health, Labor and Welfare, in addition to materials in question-and-answer format that deal with influenza, hepatitis C, and hepatitis B, to alert member physicians.

For the general public, JMA has been providing “open lectures for citizens” that are telecast on NHK-TV, and has developed handbooks such as “A Handbook Companion to Traveling Abroad” and the “Animal-borne Infectious Diseases Handbook” as well as campaign posters and pamphlets concerning prophylactic vaccination for influenza, tuberculosis, rubella, and measles.

In addition, “children’s preventive vaccination week,” a campaign scheduled for March 1 to March 7, was initiated in 2004 and will be held annually to improve regular vaccination rates.

Key words Risk management, Infectious diseases, Preventive vaccination, SARS

Establishment of the Risk Management Task Force on Infectious Diseases

Based on the increasing importance of measures to counter emerging infectious diseases such as AIDS and Ebola hemorrhagic fever, for which no decisive treatment has been established; the re-emergence of infectious diseases such as tuberculosis and malaria; and the fact that many lives have

been lost as a result of epidemics of enterohemorrhagic *Escherichia coli* (O157) infection and influenza, the Japan Medical Association (JMA) established the Risk Management Task Force on Infectious Diseases (the Task Force) within the organization on January 21, 1997.

The specific activities of this Task Force include the following:

- (1) Promotion of preventive activities including prompt provision of the latest information on infectious diseases.

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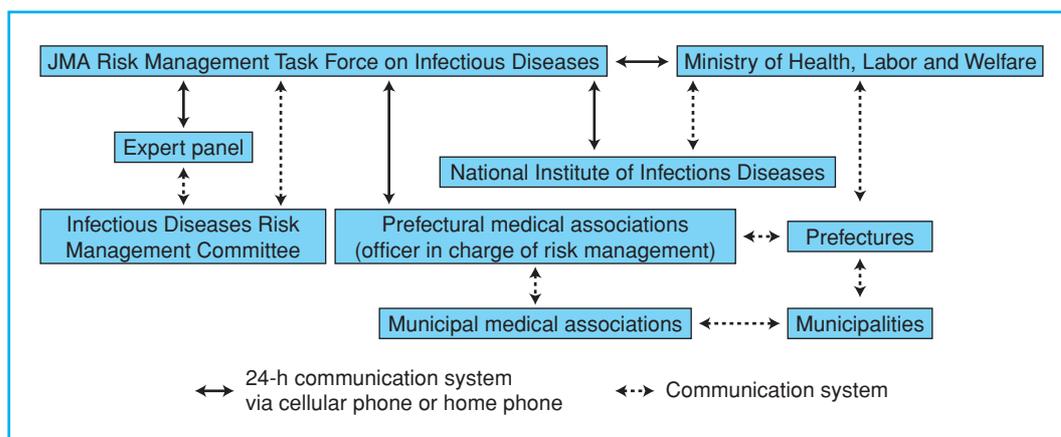


Fig. 1 Risk management system of JMA at the occurrence of infectious diseases

- (2) Provision of information regarding the diagnosis and treatment of infectious diseases, under the guidance and advice of experts in the field.
- (3) In the case of occurrence of infectious diseases with critical properties, implementation of risk management including prompt provision of information regarding the infection's occurrence, the methods of diagnosis and treatment, and the establishment of a support system.
- (4) Timely collection of information about the occurrence of infectious diseases in local areas, using the Internet and other sources of information.

Preparation of Information Provision Network

A network that will quickly provide all JMA members and general public with information about infectious diseases has been organized, with the Task Force playing the central role.

(1) In order to promote the bidirectional exchange of information with prefectural medical associations, each association was requested to designate an officer in charge, and a list of these designees was drawn up in order to construct a round-the-clock system of cooperative action using cellular phones

and other means of communication. Information sent from JMA to the prefectural medical associations is then sent to each municipal medical association and to each medical association member. All informational contacts are set up to operate bidirectionally (Fig. 1).

Information shared by members of the network will be brought to the national level through individual medical facilities and patients.

(2) A communication network has been set up among prefectural medical associations, the National Institute of Infections Diseases, the Ministry of Health, Labor and Welfare, the Narita Airport Quarantine Station, and others, and the information obtained is disseminated almost on a daily basis from the Task Force to prefectural medical associations via e-mail and facsimile and is published on the JMA website under the heading "Information on infectious diseases and food poisoning."

Infectious Diseases Risk Management Committee

The Infectious Diseases Risk Management Committee was organized by JMA to include experts on various infectious diseases who are working in the first line of defense and

four members from the executive board of JMA (including the director of the Task Force). The trends of infectious diseases in question and effective preventive measures are discussed in this committee whenever necessary.

A number of issues have been dealt with in this committee, including enterohemorrhagic *E. coli* (O157) infection, influenza, certified eradication of poliomyelitis, sexually transmitted diseases, relief from the health hazards of preventive vaccinations, measles prevention, amendment of the Preventive Vaccination Law, hepatitis C infection, severe acute respiratory syndrome (SARS), and rubella infection.

Infectious Diseases Risk Management Conference

The prefectural medical associations convene annually for the Infectious Diseases Risk Management Conference. The conference focuses on infectious diseases that are important at the time. Among the recent themes of the conference, SARS was discussed twice in 2003, while other topics have included “Recent topics in infectious diseases” in 2002, “Measures against biological weapons” in 2001, and “Current status and future issues in the diagnosis of tuberculosis and other infectious diseases.”

In addition, the following special meetings were held:

1. Conference of Local Medical Associations Related to the Site of World Cup Soccer (May 10, 2002)

Because the FIFA World Cup Soccer championships were held in Japan, the Conference of Local Medical Associations Related to the Site of World Cup Soccer was held. JMA established a special headquarters to address issues related to the World Cup, and maintained daily 24-hour information exchange during the tournament, with executives in charge assigned to prefectural medical associations of the host cities.

2. Reporting session on the prevention and treatment of SARS in China (November 5, 2003)

Following a meeting with physicians and nurses who had actually attended patients with SARS at the China-Japan Friendship Hospital, a reporting session was held in cooperation with the Japan-China Medical Association in order to help counter SARS in Japan.

Implementation of JMA Open Lectures for Citizens

The most important factor in initiating effective countermeasures for infectious diseases is to provide accurate information on them to the general public and to enlist the public's cooperation in their prevention and early detection. Because of this, JMA has been providing open lectures for the general public. This initiative has been favorably received.

The topics of recent lectures have included “Animal-borne infectious diseases” (2004), “Preventing infectious diseases by prophylactic vaccination” (2003), “Overseas travel and infectious diseases” (2002), “Insidious sexually transmitted diseases: prevention and treatment” (2001), and “A new age in infectious diseases: reconsideration of prevention and treatment” (2000). Lectures are telecast to the entire country in a 70-min program, “Saturday Forum,” on NHK TV, and are recorded on video and distributed to each prefectural and municipal medical association. These videos are available for medical association members through the lending service of the JMA Video Library.

Provision of Medical Information to Members

1. Written information

- (1) Information on infectious diseases and food poisoning
- Information on the trends, prophylaxis, diag-

nosis, and treatment of infectious diseases is collected from prefectural medical associations, the National Institute of Infectious Diseases, the Ministry of Health, Labor and Welfare, and the Narita Airport Quarantine Station, among others, and compiled into reports issued on an almost daily basis. The reports are provided by the JMA Risk Management Task Force on Infectious Diseases, and they numbered 1,700 as of November 2004.

(2) Publication of guidelines for the diagnosis and treatment of infectious diseases

In 1999, together with the enforcement of the new Infectious Diseases Control Law, “Guidelines for the diagnosis and treatment of infectious diseases” were published under the supervision of JMA and the then Ministry of Health and Welfare, and distributed to all members. Since then, however, emerging and re-emerging infectious diseases have become problematic, and supplements and revisions were issued for smallpox and anthrax in 2001, tularemia, botulism, and west Nile fever in 2002, and severe acute respiratory syndrome in 2003. In 2004, an overall revision was made in preparing “2004 guidelines for the diagnosis and treatment of infectious diseases.”

(3) Publications in the Journal of the Japan Medical Association

Relevant information has been published in “the Journal of the Japan Medical Association” to alert all member physicians. Major articles of this kind have included the following:

- A guide to enterohemorrhagic *Escherichia coli* (O157) infection for primary and secondary medical institutions
- A guide to the prevention of nosocomial infection with tuberculosis
- A guide to the prevention of nosocomial infection with influenza (prepared annually)
- Hepatitis C Q & A (revised 5th ed.)
- Hepatitis B Q & A
- Influenza Q & A (prepared annually)

2. Use of the Internet

Among the notifications sent to the respective prefectural medical associations, those of particular importance and requiring distribution to all members are published on JMA’s website.

“Guidelines for the diagnosis and treatment of infectious diseases” is available to JMA members in the form of a PDF document from this website.

In addition, relevant topics are promptly published to provide timely information; the topics which have previously appeared include “Measures against infectious diseases at the World Cup,” “On the series of terrorist attacks in the USA,” “Nosocomial infection with *Serratia* bacteria: prevention of mass infection in hospitals,” “Creutzfeldt-Jakob disease and mad cow disease (bovine spongiform encephalopathy),” “Comprehensive measures against influenza,” “Hand-foot-mouth disease Q & A,” “Does polio vaccine cause poliomyelitis?” and “Warnings about food poisoning.”

3. Use of videos

JMA open lectures for the public and discussions from the Infectious Diseases Risk Management Conference are recorded on video, distributed to prefectural and municipal medical associations, and made available to all members through the lending service of the JMA Video Library.

Education of the General Public

To provide the general public with relevant information from all of its members’ medical institutions, or through the various meetings of individual medical associations, JMA has developed the following materials:

- A handbook companion to traveling abroad
- Tuberculosis prevention campaign posters and pamphlets
- Influenza prevention campaign posters and pamphlets



Fig. 2 Campaign poster touting preventive vaccination for measles

- Prophylactic rubella vaccination campaign posters
- Prophylactic measles vaccination campaign posters (Fig. 2)
- Prophylactic vaccination promotion posters

Information on infectious diseases is provided to newspapers, television stations, and book publishers, as well as to publishers of advertisements.

Establishment of “Children’s Prophylactic Vaccination Week” (Fig. 3)

Seven disease entities are prescribed as type 1 in the Preventive Vaccination Law: diphtheria, pertussis, poliomyelitis, measles, rubella, Japanese encephalopathy, and tetanus. Type-2 diseases include influenza (target subjects are 65 years old or older). Another disease similarly requiring preventive vaccination is tuberculosis (BCG), as prescribed in the Tuberculosis Prevention Law.

Vaccination has caused a marked decrease in the number of patients with infectious diseases. In particular, the occurrence of new cases of infection with natural strains



Fig. 3 “Children’s Preventive Vaccination Week” poster

of poliomyelitis virus has been eradicated. However, recently, the overall vaccination rate has tended to decline, resulting in various problems. Various factors seem to be involved in the declining rates, among them the use of MMR (mixed vaccine of measles, mumps, and rubella), health hazards created by the gelatin used as a stabilizer in vaccines, legal amendments including altered periods of vaccination, change from obligatory to nonbinding vaccination, change from mass to individual vaccination, decreased recognition of the importance of preventive vaccination, and the changing family situation, including increasing numbers of working mothers.

The problem of health hazards was largely resolved by discontinuation of the MMR vaccine, improvement of vaccines, and the use of gelatin-free vaccines. However, in terms of revisions, further efforts will be necessary to fully implement these new systems in society.

Particular attention has been given recently to the issue of childcare, and a “children’s preventive vaccination week” was established. This campaign was aimed at drawing the attention of caretakers and

residents in the community to preventive vaccination, thereby improving vaccination rates. Special emphasis was placed on the eradication of measles in Japan and altering Japan's current reputation as an exporter of measles.

This campaign was implemented by JMA and the Japan Pediatric Society and was supported by the "Healthy Parents and Children 21" Promotion Conference. The campaign was held for one week from March 1 to March 7, 2004, a suitable period for cautioning against failure to have children vaccinated because parents' attention to vaccination is heightened during this period, which is just prior kindergarten and school entry in Japan.

During this campaign, vaccinations based on the Preventive Vaccination Law, particularly those focusing on measles vaccination, were given. Offices were open seven days a week to provide counseling and vaccinations for those who find it difficult to visit a clinic during the work week.

"Children's preventive vaccination week" was started in 2004, and will be held annually.

In 2004, this vaccination week was implemented in about 7,000 medical institutions nationwide, and the total number of vaccinees was about 13,000.

Measures against SARS

It is, of course, necessary to take all possible measures to be prepared for infectious diseases, regardless of when and where they occur.

Although SARS has not been experienced in Japan, the specific characteristics of the disease make it necessary to take measures according to the following levels of probability of occurrence: first level (normal circumstances), second level (occurrence of SARS outside the country), third level (domestic occurrence of SARS).

Risk management measures are summarized below according to the level of



Fig. 4 Japan Medical Association-recommended three-item SARS patient transfer kit

probability.

1. First level (normal circumstances)

(1) Preparedness of medical institutions

i) Preparedness of medical institutions that allow in-hospital care of SARS patients:

A total of 739 negative pressure beds have been prepared in 287 institutions nationwide (as of May 2003). Provision of information to all medical institutions is necessary, after confirmation at each prefecture.

ii) Preparedness of medical institutions that can cooperate in SARS outpatient care:

Only about 100 medical institutions are designated for infectious diseases (type 1, type 2) that would permit SARS outpatient care. Because this number would not be sufficient for the treatment of all cases, an emergency subsidy was given to 527 non-designated medical institutions that accepted the request for cooperation. The subsidy has been extended to more institutions, and a total of 759 medical institutions (as of October 2003) are prepared to handle SARS outpatient care.

iii) Preparation of general medical institutions (dealing with unexpected patient visits):

In principle, patients with suspected SARS should call a general medical institution or local public health center in advance and visit a cooperating medical institution for

outpatient care. However, when a patient has visited a general medical institution without knowing of his or her disease, the institution should, as a rule, notify the local public health center promptly and ensure that the patient is transferred to a designated or cooperating medical institution.

For this purpose, patient transfer kits consisting of a mask (N95), gown, and gloves (the JMA-recommended SARS three-item patient transfer kit) are distributed to all the local medical associations. The Japanese government also provides each public health center with 100 kits to keep in storage (Fig. 4).

(2) Physicians' training

In the SARS outbreak in Kangtong, China, more than 30% of patients were medical personnel, and the so-called "superspreader" responsible for the worldwide dissemination of SARS was reported to be a doctor. In addition, the SARS scare that occurred in Japan in 2003 was derived from a foreign doctor.

It is the responsibility of physicians, as medical professionals, to have accurate knowledge and awareness of SARS, to face the issue head-on, and to reassure the general public.

(3) Improvement of information network

Through the JMA infectious diseases information network, bidirectional information exchange with JMA members and close exchange of information with the Ministry of Health, Labor and Welfare, the National Institute of Infectious Diseases, and other relevant organizations, are being promoted to construct an effective risk management system.

(4) Countermeasures for influenza in the elderly and medical personnel (vaccination)

2. Second level (occurrence of SARS outside the country)

(1) Enhancement of the strategy to "stop SARS at the border"

It is most important to implement the strategy to "stop SARS at the border" to thor-

oughly prevent the disease from entering Japan, using the revised and strengthened Infectious Diseases Control Law and Quarantine Law.

(2) Telephone counseling to guide SARS patients to cooperating medical institutions

Medical institutions and public health centers should be aggressive in providing telephone counseling services and guiding patients to visit a cooperating medical institution for SARS outpatient care if they have a fever of 38°C or higher and respiratory symptoms such as coughing and shortness of breath in addition to being within 10 days of returning from an area where SARS is epidemic or having had close contact with a SARS patient.

(3) Thorough provision of SARS information

It is important to promptly provide medical institutions and the general public with detailed information on the occurrence of SARS in foreign countries, and to make certain that people suspected of having SARS call a local public health center or medical institution for counseling.

(4) Designation of regions of focused attention and enhanced preventive measures

Areas expected to be the site of entry of SARS should be designated as regions of focused attention, and surveillance and preventive measures in these areas should be enhanced.

(5) Setting up a headquarters for countermeasures

At the second level, a JMA SARS countermeasures headquarters has been set up to gather information from the Ministry of Health, Labor and Welfare, the National Institute of Infectious Diseases, quarantine stations, medical institutions, and so on. The relevant information is published in a collected form entitled "SARS-related information" in the daily report on "information on infectious diseases and food poisoning," to promote wide dissemination of information. The countermeasures headquarters has

implemented 24-hour correspondence.

3. Third level (occurrence of SARS inside the country)

Physicians should do their best to detect SARS in the early stage and make every effort to contain it completely by prompt reporting of the infection.

It is assumed that containment of SARS as a type-1 infectious disease may sometimes require restrictions such as closing institutions, limiting the work of medical personnel, and restricting traffic. Although it is inevitable that medical institutions will have to make some sacrifices, they should take the lead in cooperating to minimize the infection. We also consider that their sacrifice should be compensated in some way.

Measures against Large-Scale Infectious Diseases (Counter-Terrorism Measures)

Guidelines for the diagnosis and treatment of anthrax, smallpox, tularemia, and botulism, which are likely to be used as tools of bioterrorism, were developed and published in Journal of the Japan Medical Association to alert all JMA members.

In particular, measures against smallpox were discussed in the issue on “actions to be

taken against biological weapons,” and a video of measures against smallpox was produced and distributed to prefectural and municipal medical associations and has also been distributed on the Internet.

In addition, CD-ROMs describing the method of diagnosis of these infections were sent to municipal medical associations to ensure that all members are aware of them. A description has also been published on the JMA website.

Conclusion

Infectious diseases have continued to create new medical problems, not allowing caution to be relaxed. Recent years especially have seen many issues related to emerging and re-emerging viral infections. Threats from the development of highly virulent avian influenza and other new types of influenza as well as SARS have created a great deal of uneasiness among the general public.

It is the duty of medical professionals to do their utmost to diagnose and treat these infectious diseases early, and to take prompt measures against the diseases in cooperation with personnel both inside and outside the country, in order to reassure the general public as soon as possible. The public expects no less of us.

Problems of the Law on Organ Transplant and the Situation of Organ Transplantation in Japan

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Key words Organ transplant, Brain death, Diagnosis of brain death, Bioethics, Organ donor, Human rights of children

Introduction

This article outlines the situation in Japan, where organ transplantation is making very slow progress, and discusses what can be done to facilitate smooth performance of organ transplantation.

The Law on Organ Transplant was enacted in 1997. This Law was a private member's bill and subject to a free vote to reflect the independent will of each House member, and passed the House of Representatives and the House of Councilors. Article 2 of the supplementary provision of the Law states, "Concerning organ transplantation according to this Law, a comprehensive review should be made considering the actual implementation of the Law and necessary measures should be taken by approximately 3 years after implementation of this Law." However, no amendment has been enacted to date, and defects in the Law and problems in the application of the Law are hindering the progress of organ transplantation in Japan, as compared with the situation in other countries. The sections below consider the treatment of this Law in the legislative body, focusing on whether and how the Law is expected to be amended.

Present State and Problems of Organ Transplantation

Because this Law was enacted based on a free vote of House members, any amendment to it should also be based on a free vote of House members. This Law deals with life and death issues. The votes of individual House members would depend on their views concerning such issues as life and death, the right to die with dignity, religion, and ethics. For this reason, a unanimous vote cannot be expected.

One of the most difficult problems is the change of Diet members. The House of Representatives is dissolved approximately every 3 years, and subsequent general election usually results in the replacement of about one-third of House members. The discussion with new House members must be restarted from the beginning, and any draft amendment developed through past discussion would be returned to the starting point. The House of Councilors is not dissolved. While the term of members is 6 years, election of half the members takes place every 3 years, and this results in replacement of some members. For this reason, the Investigation Committee on Brain Death, Bioethics, and Organ Transplants of the Liberal Democratic Party, which is the

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ruling party, has examined the amendment of these proposals. However, the Law has been left unamended for much longer than 3 years after its enactment in 1997, and the legislative organ is responsible for this neglect of duty.

One of the key issues is the treatment of children under the age of 15. The Guidelines Concerning the Use of the Law on Organ Transplant contain provisions defining the age and other requirements for expressing wishes in writing. Organ transplantation from brain-dead donors under the age of 15 is not conducted in Japan, because the Guidelines specify that the wishes of persons at the age of 15 years or older should be respected, in concordance with the definition of ability to leave a will under the Civil Law. The Guidelines also specifies that legal determination of brain death should not be performed for the time being in the case that the potential donor is found to have mental retardation. This provision does not mention the age of the potential donor. These Guidelines effectively prohibit organ transplantation from brain-dead bodies under the age of 15.

Comparison with Situation in Other Countries

The situation in other countries is considered in this section. In many countries, including France, Sweden, the U.K., Australia, Germany, Denmark, Korea, Taiwan, and some states in the U.S., organ transplantation is permitted provided that the potential donor has expressed the wish to donate organs and the consent of relatives has been obtained. If the wishes of relatives are unknown, the consent of the potential donor alone is sufficient for performing transplantation. If the wishes of the potential donor are unknown, transplantation is possible if the consent of relatives is obtained. In France and some other countries, transplantation is allowed when the wishes of the potential donor and those of relatives are both unknown. When either the potential donor or relatives have refused, transplantation is usually not performed. In

the case of children, most countries permit transplantation if the consent of relatives is obtained. In contrast, transplantation from child donors is not permissible in Japan.

Thousands of heart transplants are performed every year worldwide, including 2,198 cases in the U.S. (2000), 342 in France (2001), 217 in the U.K. (2000), 380 in Germany (2002), 41 in the Netherlands (2002), 70 in Australia (2002), 30 in Denmark (2002), 316 in Italy (2001), 314 in Spain (2001), 26 in China (2000), and 14 in Korea. In sharp contrast to the over 2,000 cases in the U.S., the number of cases in Japan was 3 in 1999 and 3 in 2000.

The number of patients in the waiting lists for organ transplantation in Japan is 74 for the heart, 79 for the lungs, 78 for the liver, 12,549 for the kidneys, 93 for the pancreas, and zero for the small intestines as of March 1, 2004. The past records of brain-death organ transplants in Japan include 21 cases of heart transplants, 18 cases of lung transplants, 25 cases of liver transplants, 2 cases of pancreas transplants, 13 cases of liver plus kidney transplants, 38 cases of kidney transplants, and 1 case of small intestine transplant; totaling 118 cases as of July 5, 2004. Thirty-one brain-dead donors provided organs in the period from October 1997 to December 2004.

As many as 30 patients under the age of 15 received heart transplantation in hospitals outside Japan, including 25 cases in the U.S., 3 in the U.K., and 2 in Germany, as of December 1, 2004. Forty-three patients (18 males and 25 females) wanted to receive heart transplantation in overseas sites after enactment of the Law.

Why There Are Few Transplants in Japan

1. Organ donation facilities

As mentioned above, heart transplants alone present many problems. We need to consider why there are few cases of transplants in Japan. One reason is the regulations concerning organ donation facilities. In Japan, organ donation must be performed in hospi-

tals falling under any of the following 4 categories: (1) hospitals attached to universities or colleges, (2) hospitals designated by the Japanese Association for Acute Medicine as centers for training preceptors, (3) hospitals designated by the Japan Neurosurgical Society as centers for training medical specialists and having adequate capabilities in terms of instructing physicians and the number of cases treated, and (4) designated emergency care centers. There are 306 designated institutions in Japan. It is a significant hurdle that potential donors cannot provide organs unless they are diagnosed as brain dead in these institutions. Unless this hurdle is lowered, patients with organ donor card cannot provide organs if they become brain dead in other medical institutions.

By the end of June 2002, there were 323 persons who were diagnosed as brain dead and had expressed their consent to organ donation. Of this total, 162 cases occurred in places other than organ donation facilities, and therefore were ineligible. Of the remaining 161 cases, 88 were reported before cardiac arrest and 73 were reported after cardiac arrest. Of the 88 cases, brain-death organ donation was performed in 19 cases, and organ donation was cancelled after legal determination of brain death in 1 case.

The remaining 68 cases did not end in organ transplantation for various reasons. The criteria of the diagnosis of brain death were not met in 23 cases. The organs were not suitable for transplantation due to other diseases in 16 cases. The consent of family members was not obtained in 14 cases. Other reasons included the attempt of resuscitation being continued before cardiac arrest, the patient's condition hindering the determination of brain death, the patient's wish to donate their body for medical research, the judgment to invalidate the patient's wishes, and the hospital ethical committee's decision to deny approval. Although there were a number of potential donors who had indicated their wishes on donor cards (in the period from October 1997 to June 2002),

only a few of them remained after strict screening and examination.

2. Organ donors under the age of 15

What are the positions of various players related to this problem? On July 23, 2003, a nonpartisan group of Diet members called Parliamentarians Union of Bioethics Study conducted a questionnaire survey concerning organ transplants from donors under the age of 15. According to the answers from 191 persons, "brain-death organ transplants from donors under the age of 15 years" was supported by a great majority, 78% of Diet members answering that it "should be made possible."

The Japanese Society of Legal Medicine has submitted the following opinion: "Appropriately and reliably diagnosed brain death should be defined as the death of a person. A patient in the state indicating brain death should be subjected to the criteria of diagnosis of brain death according to relevant criteria irrespective of whether organ donation is intended or not. If the patient is judged as brain dead, death should be declared without waiting for cardiac arrest. The legal determination of brain death does not require the patient's written wishes or the consent of family members."

Japan Federation of Bar Associations announced the following statement in October 2002: "The amendment of legislation partially negating self-determination, such as making special provisions to permit proxy consent of parents on behalf of children under the age of 15, should not be performed at present. Proxy consent of parents should be given only for the benefit of the child. Because the removal of organs never benefits the child, such proxy consent is not appropriate." In addition, the Federation reinforced its objection by stating, "In the case of children, it is virtually impossible for them to express objections, and the spirit of self-determination would be neglected."

The Japan Pediatric Society made a proposal on June 23, 2003. First, it "permits brain-

death organ transplants in children as a form of treatment.” Second, the Society stated, “As a prerequisite, we propose continued discussion of problems to improve the environment for such change.” It also proposed, “From the standpoint of protecting the human rights of children, it is desirable to promote the use of child donor cards to clarify the right of self-determination. As a prerequisite, we need to clarify the processes of informed consent concerning treatment for children, to implement educational programs concerning research and other activities, and to establish a neutral system to avoid intentional inducement. In addition, we need to train coordinators specializing in organ transplantation in children and also to lower the age limit for expressing wishes from 15 years old.” Recently, there have been some proposals to lower the age limit from 15 to 14 years old.

As a means to exclude brain-dead cases resulting from child abuse, the Society expressed the following opinion: “It has been pointed out that about 10% of children with head injury are potentially victims of child abuse. A period ranging from 2 weeks to more than 1 month may be required before the evidence of child abuse can be obtained, and the fact of child abuse may be overlooked in some cases. To exclude such cases, we need to encourage medical institutions to suspect that child abuse victims may be present among the group of injured children, and each case should be reviewed by an independent panel involving non-medical members. In particular, to avoid the danger of organ donation based solely on proxy consent given by a custodial parent, it should be clearly stated that brain-death organ donation from children is a special exception, strict procedures should be required, provisions including punishment for violations should be implemented, a specialized investigation organization should be established, and permission from such organization should be made a prerequisite.”

The President of the Japan Pediatric Society

pointed out the following problems in organ transplantation in Japan: the number of organ donations is small, persons under the age of 15 cannot donate organs, and many living organ donations are performed. He also blamed the government for the fact that some lives could have been saved.

A physician at the Department of Pediatrics, Osaka Medical College stated, “The question of whether or not brain death should be regarded as the actual death of a person still remains medically unsolved, and defining brain death as the death of a person is problematic particularly in the case of children. Permitting organ removal from children under the age of 15 based on the consent of parents would be an infringement of the human rights of children. It would run counter to the Convention on the Rights of the Child assuring the right of the child to express his or her views freely in all matters affecting the child. The percentage of child abuse is considered high among the causes of brain death in children, but measures to counter child abuse have not been worked out.” The physician also pointed out, “Major rethinking is needed on the current legal criteria of diagnosis of brain death applied to 6-year-old and older patients, as well as the draft criteria of diagnosis of brain death in children (proposed in 2001), which involve problems regarding implementation systems and the number of cases. The families of donors and prospective donors should be given sufficient explanation concerning the activities of the body in the state of brain death, the actual procedures performed in organ removal, and the changes that would occur in the body during organ removal. A consensus that brain death is the death of a person has not been reached across various disciplines, including religious circles, and among the citizens of Japan.”

A professor of child psychology at Ochanomizu University stated, “An 8- or 9-year-old child can understand the state of physical death. I have heard of no research concerning the children’s understanding of

brain death. The basic meaning of organ transplantation, that is to replace the parts of the body, can be understood at the age of about 10 or 11 years. Children would be able to make their own decisions concerning organ transplantation and other matters related to their internal organs probably at the age of about 10.”

Based on experience, a professor of laws commented on testimonies given by children as follows: “What testimony, judgment, and explanation are given by a child depends on who performs the interview and in what ways. Interviews should be conducted not only by parents but also by independent specialists well versed in communicating with children. The interview must be recorded on audio or video media. Children can understand the concept of death at the age of 4 to 5 years, depending on experience. They gain the ability of decision-making probably when they are 4th or 5th graders. I have no objection, if children can receive an adequate explanation of the merits and demerits of transplantation, they can change their minds easily, and revisions are made at one-year intervals.” As he stated, 4th or 5th graders are able to understand various complex matters.

Proposals to Amend the Law on Organ Transplant

As discussed above, people in different positions and with different academic stances have different opinions. Considering this situation, the Investigation Committee on Brain Death, Bioethics, and Organ Transplants of the Liberal Democratic Party has compiled the outline of a draft bill to amend parts of the Organ Transplant Law and submitted a set of proposals. The following sections summarize the proposed changes.

1. Prerequisites for organ removal

The first part of the proposed amendment relates to the prerequisites for organ removal. The proposed text reads as follows: “A physician may remove the organs for use in

transplantation from a dead body (including a brain-dead body), if any of the following conditions is met: (1) The deceased has expressed, in writing, the will to offer organs for use in transplantation, and either the family members of the deceased, after being notified of this fact, do not refuse the removal of organs or there are no family members of the deceased; and (2) The deceased has expressed, in writing, neither the will to offer organs for use in transplantation nor the lack of such will, and the family members of the deceased have provided written consent for the removal of the organs.” This provision would make possible organ removal when the will of the deceased is unknown.

In addition, there is a proposal stating, “The diagnosis of brain death does not require the written indication of the patient’s will or the consent of families.” At present, the process of the determination of brain death may not begin unless the patient and the families have provided written consent for beginning such process. The proposed provision would make such consent unnecessary. This translates to the notion that the determination of death should be made on a scientific basis even in the case of brain death.

Another proposal states, “The problem of whether or not brain death is the death of a person should be left to the judgment of the persons involved. Based on this understanding, organ removal should be permitted only when the deceased has expressed the will to offer organs in writing and the families do not refuse, or when the will of the deceased is unknown, in which case the matter should be left to the judgment of close relatives.”

2. Organ donation with priority given to related recipients

The second part of the proposed amendment would introduce “organ donation with priority given to related recipients.” On the basis of the above-mentioned possibility of removing organs for transplantation from a dead body (including a brain-dead body) and assuming the confirmation of the will to

donate organs, this proposal allows the written indication of the will to provide organs preferentially to the spouse or blood relatives within the second degree of kinship.

However, this notion has given rise to much controversy. The rationale for allowing organ donation in this form is respect for the will of the donor, but this respect for the will of the donor might compromise the ideal that the opportunity for receiving transplantation should be distributed equally. The scope of the relatives receiving priority is another problem. The proposal limits the scope to blood relatives within the second degree of kinship (grandparents, parents, siblings, children, and grandchildren), in addition to the spouse. In the implementation of the Law, the will expressed by persons aged 15 years or older would be respected. Concrete issues concerning the treatment and effectiveness of the will to give priority to relatives would be stipulated in the guidelines.

The proposal does not permit the indication of the will to deny donation to non-related recipients in the case that the organs are incompatible with the related recipient. However, concrete issues concerning the treatment and effectiveness of such indication of the will should be defined in the guidelines. The problem of whether or not the related recipient needs recipient registration would be treated not in the Law but in the guidelines, considering the coherence with the provisions in the existing Law. The Organ Transplant Committee of Disease Control Division, Health Sciences Council submitted the report "Treatment of the Living Will of the Donor Concerning the Recipients of Organs" to the Diet for discussion to form a conclusion. Although further debates are expected, this report provided a provisional conclusion to permit the living will to donate organs giving priority to the spouse and relatives within the second degree of kinship.

3. Issues concerning promotion and education

The third part of the proposed amendment

contains a new provision stating, "As regards the issues concerning promotion and education, the State and local public bodies should take necessary measures for education and dissemination of knowledge concerning transplant medicine, such as indicating whether or not each person has expressed the will to donate organs for use in transplantation on driver's licenses and health care insurance cards, so that the citizens can develop the understanding of and interest in transplant medicine at every opportunity." At present, donor cards are available at convenience stores and other places. The Law should be amended to encourage more people to opt to have donor cards.

Finally, the fourth part of the bill would delete the temporary provisions concerning eye and kidney transplants.

Conclusion

While the contents of the proposed amendment are as outlined above, this draft bill must be used as a starting point for discussion by the nonpartisan Parliamentarians Union for Bioethics Study and the amendment must be passed in the form of private member's bill. There will be a procedure for organ donation from donors under the age of 15 based on the consent of close relatives, and the procedures for diagnosis of brain death will be defined clearly in guidelines, such as the exclusion of infants within 12 weeks after birth. In addition, the promotion of transplant medicine will need to be supported by measures to reduce the burdens on patients, such as the expansion of health insurance coverage.

The most important thing is to save the precious lives of patients, who are waiting for the opportunity to receive an organ transplant, legally within the strict framework of regulations. It is strongly desired that the bill will be discussed and a vote taken during the ordinary session of the Diet.