JMAJ
Japan Medical Association Journal
Vol.49, No.7&8 July/August 2006

Editorial

Original Articles

Review Articles

Case Reports

Clinical Topics in Japan

Green Revolution

Naruo Uehara*1

A new variety of rice called IR8 or "miracle rice," capable of vastly increasing the rice yield per land area unit, was developed in 1966 at the International Rice Research Institute (IRRI), established in the Philippines by a U.S. foundation. The "Green Revolution," which refers to the use of new crop breeds and new farming technologies to increase cereal productivity, has been introduced and promoted by international development aid to developing countries in Asia, as epoch-making technology which helps overcome anticipated food crises to be brought by the rapid increase of population. As a result, in China, Pakistan and India, the supply of cereals has been improved, and countries such as Indonesia, Vietnam and Thailand have even become net exporters. For a while, the "Green Revolution" became a byword to symbolize the power of science and the success of technology transfer.

However, now after the passage of over 30 years, the evaluation on the effects of "Green Revolution" remains controversial.[1] In contrast to conventional crop varieties, the high yield of the new varieties was dependent upon the use of large quantities of water, agricultural chemicals and chemical fertilizers, which in turn required high levels of investment and thus enlarged the divide between rich and poor farming areas, while creating a dependence upon the market economies of advanced nations for the provision of such agricultural chemicals and chemical fertilizers. Moreover, this also helped cause the desertification of irrigated areas and pollution by agricultural chemicals, in some cases even producing conflict between communities over water. In addition, it had been hoped that the increase in productivity of cereal crops would help alleviate food shortages and thus contribute to the improvement of nutritional status of the people, consequently benefiting public health. However, Okada's review suggested that these hopes appear to have been betrayed.

It seems that although the "Green Revolution" seems to have been a success as far as the national total cereal production figures are concerned, a look at it from the perspective of communities and individual humans indicates that the problems have far outweighed the successes, leaving many lessons to be learned.

In his now classic book "Small Is Beautiful," E.F. Schumacher said "Modern agriculture relies on applying to soil, plants, and animals ever-increasing quantities of chemical products, the long-term effect of which on soil fertility and health is subject to very grave doubts."[2] Claiming that the central issue is how the technology should be, he requested scientists and engineers to pursue appropriate technology ("Intermediate Technology") instead of compelling the choice of "poison or hunger." Appropriate technology is available to everybody, not exclusively to privileged groups, and it must be useful in providing "help to those who need it most."

In the sense that technological innovation took the leading role in "development" and penetrated radically and extensively into the lives in communities for the cause of achieving the benefit it seemed to promise, the lessons from the "Green Revolution" are reminiscent of "medicalization of life" of Ivan Illich. Illich argued that the modern medicine has been causing more harm than benefit to people, despite the series of innovation of medical technologies.[3] He addressed the issue of uncertainty in effectiveness of modern medical technologies, and warned us the danger of rendering our health and survival dependent on technologies, which tended to be industry-driven, rather than human-centered.

When I encountered his admonition in 1978, I could not accept it, as being a zealous hard-working surgeon, and seriously tried to contrive a way to refute it. Now, in the face of the large body of facts of medical adverse events in Japan, as well as the reality revealed by the report from Institute of Medicine[4] and also numerous subsequent reports from many countries, I realistically understand the gravity of the Illich's words at the beginning of his book titled "Medical Nemesis"—"The medical establishment has become a major threat to health."[3]

References

1. Shiva V. The Violence of the Green Revolution: Third World Agriculture, Ecology and Politics. London: Zed Books Ltd.; 1992.
2. Schumacher EF. Small is Beautiful: Economics as if People Mattered. London: Blond and Briggs; 1973.
3. Illich I. Limits to Medicine: Medical Nemesis, the Expropriation of Health. London: Calder & Boyars; 1975.
4. Committee on Quality of Health Care in America, Institute of Medicine. To Err is Human: Building a Safer Health System. Washington DC: National Academy Press; 2000.

*1 Division of International Health (Quality & Health System), Tohoku University Graduate School of Medicine, Sendai
Correspondence to: Naruo Uehara MD, PhD, Division of International Health (Quality & Health System), Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan. Tel: 81-22-717-8197,
Fax: 81-22-717-8198, E-mail: naruo@t3.rim.or.jp

The Longitudinal Effects of the "Green Revolution" on the Infant Mortality Rate in Rural Thailand

JMAJ 49(7・8): 236–242, 2006

Yukinori Okada,*1 Susumu Wakai*2

Abstract

Objectives A rapid increase in the ratio of rented farming land to total farming land and the stratification of peasantry has been reported in rural Thailand since the 1960s. The problem is especially severe in the central region, where the commercialization of agriculture called the "Green Revolution" has been rampant with enhanced integration of agricultural resources by absentee landlords. We analyzed the problem by evaluating its effect on the health status of infants in rural Thailand.

Methods We examined three indicators; IMR, NMR and PNMR as dependent variables in relation to the ratio of rented land as independent variable. The surveyed period was between 1963 and 1998. ANCOVA analyses were applied.

Results IMR and NMR showed a statistically significant association with the ratio of rented land ($F=7.77$, $P<0.01$; $F=32.88$, $P<0.0001$). The longitudinal time-trends of IMR and NMR also showed a significant association with that of the ratio ($F=10.97$, $P<0.05$; $F=29.87$, $P<0.001$). PNMR did not show any significance.

Conclusion The ratio of rented land is a factor that reflects the extent of commercialization of agriculture and explains the substantial regional diversity of the mortality rates in Thailand. The existence of nutritional deterioration and vulnerability induced by the "Green Revolution" is suggested, since NMR reflects endogenous factors of the area and is sensitive to nutritional and sanitary conditions rather than PNMR. Further empirical studies that emphasize the linkage are necessary to attain a lower IMR in Thailand.

Key words Ratio of rented land, Green revolution, Infant, neonatal, and post-neonatal mortality rate, Nutritional deterioration

Introduction

The ratio of rented farming land to the total farming land in rural Thailand has increased rapidly since the 1960s, and the effect on the rural society has been studied.[1–10] This problem is especially severe in the central region, where the commercialization of agriculture is rampant. Numerous studies have warned of the increase in the number of landless peasants and their indebtedness to landlords.[1–4] Sein and Brouse concluded that such deteriorating land tenure problems are a major deterrent to higher productivity, resulting in the lower average rice yield of Thailand compared to that of other Asian nations.[3]

On the other hand, the World Bank has concluded that there is little evidence of exploitation and indebtedness, and the studies had exaggerated the issue.[5] Laurence surveyed two Changwats (provinces in Thailand) of the central region from 1910–1972 concluding that there was no evidence of a dramatic increase in land concentration among wealthy landlords since landlords were too heterogeneous to build

*1 Fujieda Municipal General Hospital, Fujieda
*2 Department of Community Health, School of International Health, Graduate School of Medicine, the University of Tokyo, Tokyo
Correspondence to: Yukinori Okada MD, Fujieda Municipal General Hospital, 4-1-11 Surugadai, Fujieda-shi, Shizuoka 426-8677, Japan.
Tel: 81-5-4646-1111, Fax: 81-5-4646-1122, E-mail: yokada-tky@umin.ac.jp

typical exploiting relationships with landless peasants in traditional Thai rural villages,[6] although some studies suggested that the commercialization of agriculture around the 1970s symbolized as the "Green Revolution" had restructured traditional Thai rural villages, and the inequitable distributions of resources might be expanded.[4,7–9]

While the effect of such problems has been discussed, few studies have evaluated its association with health statuses in rural Thai societies, partly because of the lack of sufficiency and credibility of the statistical data. The purpose of this research is thus to evaluate the effect of the inequitable land tenure and the "Green Revolution" on health statuses of infants in rural Thailand with the aid of both cross-sectional and longitudinal analyses.

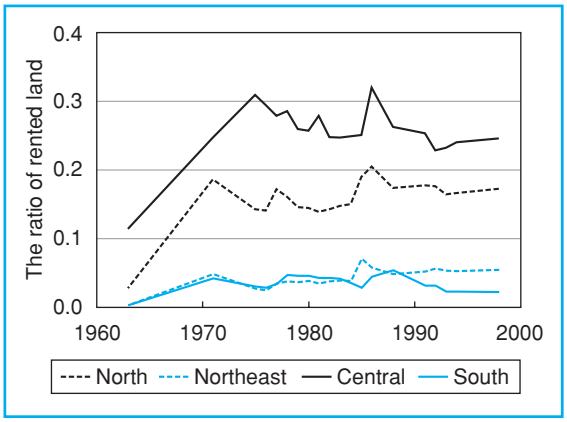

Fig. 1 The ratio of agricultural rented land to total farming land in four regions of Thailand: 1963–1998

The Ratio of Rented Land

The ratio of rented farming land to total farming land in Thailand underwent a rapid increase, particularly in northern and central regions (Fig. 1).[20,21] In 1963, the ratio was less than 5%, but increased rapidly in the 1960s and 1970s, and reached as high as 15% in 1985. Although the agricultural land reform law passed the Legislative Assembly of Thailand in 1975, the raised ratio remained high and unchanged afterward. The Thai government proclaimed that the reform was failed.[3,4] At the same time, regional diversity had widely enlarged. The central and northern regions marked rapid increase of the ratio while the northeast and southern regions maintained a low ratio of approximately 5% throughout the surveyed period.

Thailand has a politically stable history and a high proportion of the population is engaged in agriculture.[10,22] The rice export policy enhanced the commercial value of rice and the tenure of rice fields, and speculative trade on agricultural lands by absentee landlords living in urban areas has been active since the 1910s.[1,10] However, the heterogeneous relationships between peasants and landlords supported by land renting performed mostly by relatives hampered the inequitable accumulation of land to absentee landlords, and the increase of the ratio was repressed until the 1960s.[4–10]

The ratio was dramatically increased by the commercialization and modernization of agriculture in the 1970s during the so-called "Green Revolution."[4,7,9] It provided new seeds with high harvest, mechanical cultivators, fertilizers, and significant progress in land productivity was achieved. Since it demanded large-scale capital investment, which was difficult to meet for small farmers and caused soaring land prices, integration of agricultural resources (=land) by the absentee landlords and stratification of peasantry was rapidly promoted. Kitahara reported that small farmers under 20 rais (1 rai=0.16 ha) were unable to compete because of the difficulty in meeting investment demand and indebtedness.[9]

The central and northern regions have wide, flat plains with abundant rainfall. Irrigation systems double the rice yield. The commercialization of agriculture and the effects of the "Green revolution" were most evident in these two regions, especially around Bangkok in the central region.[1,4,7–10]

IMR/NMR/PNMR in Thailand

We selected infant mortality rate (IMR), neonatal mortality rate (NMR) and post-neonatal mortality rate (PNMR) as health indicators. These three mortality rates are good indicators of health statuses in developing countries, and many previous studies have suggested strong negative associations with socioeconomic and environmental factors in societies.[11–19,34] Mortality rates reflect unique characteristics of societies. While NMR is more sensitive to the sanitary

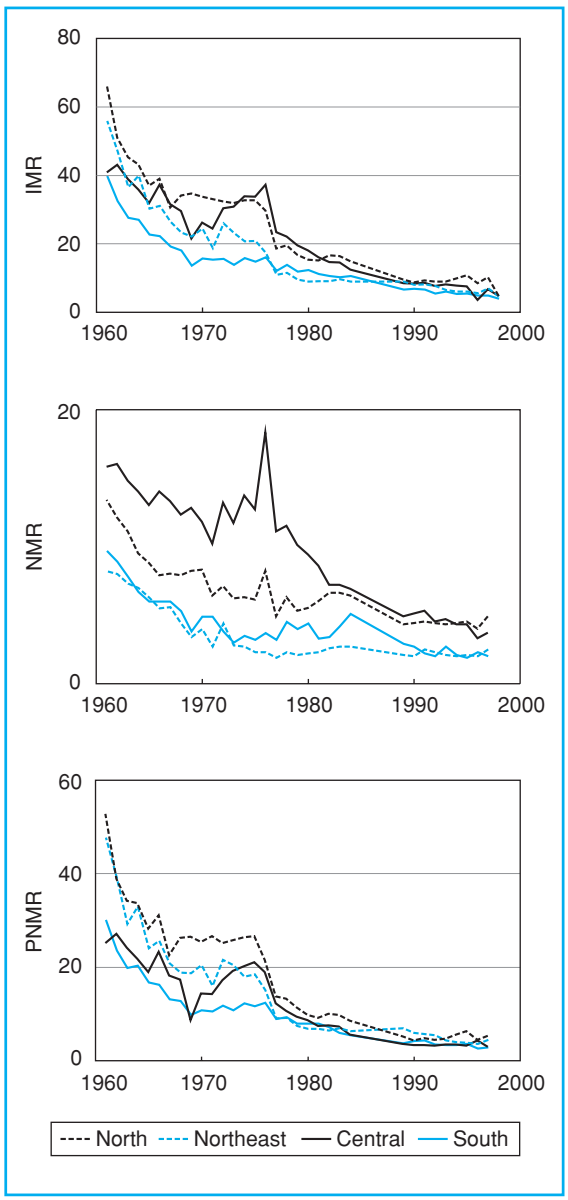

Fig. 2 Time-trends of IMR/NMR/PNMR in four regions of Thailand

IMR: Infant mortality rate; NMR: Neonatal mortality rate; PNMR: Post-neonatal mortality rate

and nutritional conditions of the area, PNMR is more sensitive to the social and economic development or the availability of health resources.[14–16,19] Within the first year, endogenous causes of death (e.g. prematurity and congenital disorders) occur mainly during the neonatal period, while exogenous causes (e.g. infectious and parasitic diseases caused by environmental factors) are responsible for deaths occurring during the post-neonatal period.[19]

Thailand has experienced a considerable decline in IMR in recent decades like other developing countries (Fig. 2).[22,23] Not only the medical technical imports from the developed world but economic growth, the development of health care systems and socioeconomic conditions have contributed to this decline.[25–27] However, substantial regional and urban-rural (municipal/non-municipal) differences exist within the country.[24–27] Children born in urban areas have a significantly higher chance of survival. Although the differences in socioeconomic development have been used to explain these diversities, typical socioeconomic factors, such as primary education and average income, have failed to explain these diversities.[24,27] Moreover, IMR marked little progress, or even recession, around the 1970s, when the "Green revolution" was in full swing. Thai society has unique socioeconomic factors. NMR and PNMR have also been in a similar situation.

Methods

Data used in this paper were obtained from the statistics and censuses published by the Thai government.[20–23] The ratio of rented land and other agricultural data were taken from agricultural statistics (published annually) and censuses (conducted in 1963, 1978, 1983, 1993), and mortality rates and population data from the Ministry of Public Health.

Although the Thai government has systematical record systems, it has suffered under-registration in vital statistics.[26,28] Gaps occurred between IMR estimated by the Ministry of Public Health and the Office of the Prime Minister.[22,24,26,28] In our research, we adopted the former because they were the only sources that covered the basic vital statistics of all four regions of rural Thailand. Analytical efforts were also made to complement imperfections in the data.

Thailand consists of four major regions and about 80 Changwats (provinces). Although these classifications were adopted in Thai official statistics, provincial data were insufficient in some variables. Since most previous studies referring to rural Thai societies put emphases on the comparisons between regions, we adopted regions as basic units of our analyses (n = 4).

Variables used in the analyses were IMR/NMR/PNMR (dependent variables), the ratio of rented farming land to total farming land (independent variable), and the ratio of population in non-municipal area (control variable). Variables were calculated from the data for every year of the surveyed period 1963–1998. There were, however, lags in the data because of restrictions in the data available. Most of the following analyses were applied for the years when necessary data were available.

Although we firstly adopted other typical indicators as control variables, including household income and the extent of maternal education, our previous research did not show any significant association between these indicators and IMR, except for the ratio of population in non-municipal areas, as some documents pointed out.[24,27] Thus, the ratio of population in non-municipal areas was finally adopted as the control variable in addition to the year and region. Since the urban-rural diversity of the mortality rates was substantial in Thailand, the Thai government divided all country areas into municipal (=urban) and non-municipal (=rural) areas, and the ratio of population in non-municipal areas had been recognized as the most influential factor in determining the mortality rates in previous studies.[24–27]

After we checked the correlation among the variables and certified the suitability of the model for multi-variant analysis, we performed the ANCOVA (analysis of co-variance) tests to analyze a more integrated association between them.

Since the ratio of rented land and the effect of the "Green Revolution" had not been directly associated with the mortality rates in Thailand, we also evaluated the association among the longitudinal time-trends of these variables to achieve further analysis, in addition to the non-trend evaluations. To smooth data and clarify the time-trends of the variables, we divided the whole surveyed term, 1963–1988, into three terms (1963–1975, 1975–1985, 1985–1998) in accordance with the situation of Thai agricultural and the governmental policy. The land reform law was passed in 1975, and it was rethought in 1985 because of its insufficient impact. For these three terms, the slopes of each variable were calculated from liner regression. They were defined as new variables, which reflected the longitudinal movements of the original variables, or whether they were increasing or decreasing. As for the mortality rates, slopes were calculated from log-linear regression to control their natural decline. The correlation check and ANCOVA tests were also applied for these new variables in the same way as the non-trends analysis. (Twelve measurements for three terms and four control variables.) We used Stat 8.0 for analyses. The study design was approved by an ethics review board.

Results

The correlation tests showed significant association between variables, and verified that our model was appropriate for ANCOVA tests.

Table 1 and 2 show the results of the ANCOVA tests. The associations of the variables are summarized in Table 1, and the associations between the longitudinal time-trends of the variables are summarized in Table 2. Region and year were treated as categorical variables, and the others as numerical variables. In longitudinal time-trends analysis, region was omitted from the control variables because of the fitness of the models. All the models marked R^2 more than 0.80.

In Table 1, the ratio of rented land had a significant association with IMR ($F=7.77$, $P<0.01$) and NMR ($F=32.88$, $P<0.0001$), but not with PNMR. The year had a significant association with all mortality rates. Although the control variables had a significant association with NMR, their F values were less than that of the ratio of rented land. This suggests that the ratio of rented land significantly associates with IMR and NMR through the surveyed period compared to other control variables.

In Table 2, longitudinal time-trends analysis shows similar results. The slopes of the ratio of rented land had a significant association with those of IMR ($F=10.97$, $P<0.05$) and NMR ($F=29.87$, $P<0.001$), but did not have such an association with PNMR. The period had a significant association with all mortality rates. Although the slopes of the ratio of the population living in non-municipal areas had a significant association with those of NMR, its F value was less than that of the ratio of rented land, and this gap was wider in longitudinal time-trends analysis than in non-trend analysis. This suggests that the longitudinal movement of the ratio of rented land also links more significantly

Table 1 Results of ANCOVA test applied for IMR/NMR/PNMR

		IMR	NMR	PNMR
Number of observations		68	64	64
Root MSE		3.210	1.310	2.466
R-squared		0.918	0.899	0.914
Adj R-squared		0.881	0.852	0.874
F value	Model	24.64**	19.1**	22.76**
	The ratio of rented land	7.77**	32.88**	0.87
	Year	7.36**	2.63**	9.33**
	Region	0.72	9.58**	0.54
	The ratio of population in non-municipal areas	3.25	20.33**	0.09

**: $P<0.01$
IMR: Infant mortality rate; NMR: Neonatal mortality rate; PNMR: Post-neonatal mortality rate

Table 2 Results of ANCOVA test applied for longitudinal trends of IMR/NMR/PNMR

		IMR	NMR	PNMR
Number of observations		12	12	12
Root MSE		0.015	0.019	0.024
R-squared		0.848	0.857	0.824
Adj R-squared		0.762	0.775	0.724
F value	Model	9.78**	10.46**	8.19**
	The ratio of rented land	10.97*	29.87**	4.10
	Period	7.06*	14.34**	6.8*
	The ratio of population in non-municipal area	2.46	6.51*	1.00

**: $P<0.01$, *: $P<0.05$
IMR: Infant mortality rate; NMR: Neonatal mortality rate; PNMR: Post-neonatal mortality rate

to that of IMR and NMR than to other control variables.

These results suggest significant longitudinal associations between the ratio of rented land and IMR/NMR in rural Thailand, and the ratio is a better indicator than the previous discussed control variables. Although IMR and NMR marked a general progression throughout the surveyed term, they show a temporal stagnation around the 1970s especially in the central region. Our results suggest that this stagnation is significantly associated with the rapid rise in the ratio of rented farming land, reflecting the negative effects of the "Green Revolution."

Discussion

Since NMR reflects the endogenous factors of the area and greater sensitivity to nutritional and sanitary conditions rather than PNMR,[14,16–19] our results indicate substantial longitudinal linkage from the rapid increase of the rented land to the temporary recession of IMR/NMR, and finally to the nutritional and sanitary deterioration in the rural area of Thailand in the 1960s and 1970s.

Sociological studies on Thai rural communities indicate this linkage. The formation of typi-

cal landlordism itself is unsatisfactory to explain the linkage. Paul DF and Dennis PH reported that the IMR for children born to small farmers and farm laborers in rural Thailand was nearly the same as that of children born to landlords and did not reflect the income differences.[28] Despite previous studies that predicted the disaggregation of rural hierarchy,[4,7,9] no substantial change in the distribution of farm size is reported in Agricultural Censuses of Thailand.[21] The high ratio of rented land in Thailand might have been achieved without forming landlordism, and the linkage which our results suggest would integrate downward pressure to entire rural societies rather than inequalities within each villages.

Instead of typical landlordism, the commercialization of agriculture accelerated by the "Green Revolution" complements our linkage to endogenous deterioration. Some researches have reported nutritional deterioration and vulnerability caused by the introduction of commercialization of agriculture.[29–33] The shift to cash cropping destroys traditional farming, which provides nutritionally balanced diets to buffer seasonal shortfalls. It also leads to high income dependence on international pricing policy of cash crops, and instabilities of the prices increase the vulnerability. Children of the households engaged in small sized farming are most sensitive to the vulnerability, and greater morbidity among children is reported.[33] Although higher productivity is achieved, increased income is not translated directly into nutritional condition because of increased expenditure and deprivation from non-agricultural capital though price controls. Kitahara J noted that the rapid rise of gas prices and the low price of rice controlled by the Thai government affected rural farmers severely despite the rise in average incomes in Thailand.[9] Thus, it has been suggested that the rapid penetration of commercialized agriculture, or the "Green Revolution," caused a deterioration in the nutritional and sanitary vulnerability in rural Thai society, especially around the 1970s.

The high ratio of rented land reflects the extent of commercialization of agriculture. Michel L noted the concentration of land and the displacement of marginal and landless farmers as being important consequences of the "Green Revolution."[29] Our results also suggest that the ratio of rented land is a good indicator of IMR/NMR and explains substantial regional diversity of these mortality rates in Thailand compared to the conventionally discussed indicators.

In the course of economic development, the negative aspects of the "Green Revolution" for rural dwellers had not been emphasized. Further discussion from various aspects is necessary to explore this issue. The incomplete government statistics and following methodological restrictions need to be overcome by analyses in based on thorough empirical committee based research.

In addition to regional and urban-rural disparities, substantial international gaps of IMR between developing and developed countries still exist even in the 21st century. On the other hand, the commercialization of agriculture is now strongly promoted worldwide to improve self-sufficiency in food products.[34] The results of our study indicate the importance of evaluating health status of community residents in the course of rapid induction of commercialized agriculture, and also contribute to following researches and enhancement of public health policy towards attaining lower IMR not only in rural Thailand but also in other developing countries.

References

1. Steven P. Sources of stability and instability in rural Thai society. J Asian Stu. 1968;27:777–790.
2. Jack MP. Thai Peasant Social Structure. Chicago and London: The University of Chicago press; 1976.
3. Sein L, Bruce E. Agrarian Reform in Thailand: Problems and prospects. Pac Aff. 1976;49:425–442.
4. Matsuda T, Kanazawa N. Tai inasakuno keizaikouzou [Economic structure of Thailand rice cropping]. Tokyo: Association of Agriculture and Forestry statistics; 1990. (in Japanese)
5. World Bank, Thailand: Case Study of Agricultural Input and Output Pricing. Washington: World Bank Staff Working Paper No.385; 1980.
6. Laurence DS. Patterns of land ownership in central Thailand during the twentieth century. J Siam Soc. 1976;64:237–274.
7. Oono M. Asiano-nouson [Asian agricultural committee]. Tokyo: Tokyo University press; 1969. (in Japanese)
8. Umehara H, Kosuke M. Tonan Ajia Nosonkaiso no Hendo [Agrarian Differentiation in Southeast Asia]. Tokyo: The institute of developing economies; 1993. (in Japanese)
9. Kitahara J. Tainouson no kouzou to hendou [Structure and Changes in Thailand agricultural committee]. Tokyo: Keiso press; 1987. (in Japanese)
10. Watanabe A. Tounan-asia [Southeast Asia]. Tokyo: Asakura press; 1971. (in Japanese)

11. Hobcraft JN, McDonald JW, Rutstein SO. Socioeconomic factors in infant and child mortality: A cross-national comparison. Pop stu. 1984;38:193–223.
12. Jayachandran J, George KJ. Socioeconomic development, medical care, and nutrition as determinants of infant mortality in less-developed countries. Soc Bio. 1986;33:301–315.
13. Jacob AA. Infant mortality in Nigeria: Effects of place of birth, mother's education and region of residence. J biosoc sci. 1994; 26:469–477.
14. Kees M, Roland B, John SK. Socio-cultural determinants of child mortality in southern Peru: Including some methodological considerations. Soc Sci Med. 1993;36:317–331.
15. Bimal KP, Deborah JR. Utilization of health facilities and trained birth attendants for child in rural Bangladesh: an empirical study. Soc Sci Med. 2002;54:1755–1765.
16. Bimal KP. Health service resources as determinants of infant death in rural Bangladesh: as empirical study. Soc Sci Med. 1991;32:43–49.
17. Shushum B. Patterns and causes of neonatal and postneonatal mortality in rural Bangladesh. Stud Fam Plan. 1989;20:136–146.
18. Jeffrey BG, Becky D, Susan L. Socioeconomic differentials and neonatal mortality: Racial comparison of California singletons. Pediatrics. 1989;83:181–186.
19. Dudley L, Poston Jr, Richard GR. Toward a reformulation of the neonatal mortality rate. Soc Bio. 1985;32:1–12.
20. Ministry of Agriculture, Government of Thailand. Agricultural statistics of Thailand. Thailand: Ministry of Agriculture, Government of Thailand; 1963–1998.
21. Office of the Prime Minister, Government of Thailand. Thailand census of agriculture. Thailand: Office of the Prime Minister, Government of Thailand; 1963,1973,1983,1993.
22. Office of the Prime Minister, Government of Thailand. Population and Housing Census. Thailand: Office of the Prime Minister, Government of Thailand; 1960,1970,1980,1990,2000.
23. Ministry of Public Health, Government of Thailand. Public Health Statistics. Thailand: Ministry of Public Health, Government of Thailand;1963–1998.
24. John K, Apichat C. Infant and child mortality in Thailand: levels, trends, and differentials as derived through indirect estimation techniques. Honolulu: East-West Center; 1978.
25. Paul DF, Dennis PH. The impact of class, education and health care on infant mortality in a developing society: The case of rural Thailand. Demography. 1982;19:391–408.
26. Apichat C. Mortality Trends and Differentials in Thailand: 1950–1975. (Presented in Mortality in South East Asia: a review of changing trends and patterns, 1950–1975.) Manila: WHO/ESCAP; 1980.
27. Ogawa N, Gavin WJ, Jeffrey GW. Human Resources in Development along the Asia-Pacific Rim. New York: Oxford University Press; 1993.
28. Lumbiganon P, Panamonta M, Laopaiboon M, Pothinam S, Patithat N. Why are Thai official perinatal and infant mortality rates so low? Int J Epidemiology. 1990;19:997–1000.
29. Michel L. New seeds and poor people. London: UNIWIN HYMAN; 1989.
30. Kathleen MD. Income and dietary adequacy in an agricultural community. Soc Sci Med. 1983;17:1877–1786.
31. Kathryn GD. Nutrition and the commoditization of food systems in Latin America and the Caribbean. Soc Sci Med. 1989;28: 415–424.
32. Deborah FB. Nutrition and the commoditization of food in Sub-Saharan Africa. Soc Sci Med. 1989;28:425–440.
33. Kathleen MD. Nutrition and the commoditization of agriculture: Ten years later. Soc Sci Med. 1993;36:1407–1416.
34. United Nations. Human Development Report 2003. New York: United Nations Publications; 2003.

Original Article

Symptom Experience and Patterns of End-of-Life
—Home care for elderly patients with cancer vs. those without cancer in Japan

JMAJ 49(7・8): 243–250, 2006

Yoshihisa Hirakawa,[*1] Yuichiro Masuda,[*1] Masafumi Kuzuya,[*1] Takaya Kimata,[*1] Akihisa Iguchi,[*1] Kazumasa Uemura[*2]

Abstract

Background The aim of this study was to assess and compare the frequency of symptoms and the receipt of end-of-life care between elderly patients with and those without cancer who spent the last two days of their lives at home.

Methods The present data were obtained from the Dying Elderly at Home (DEATH) project, a multicenter observational study. The subjects of the study were 240 consecutive decedents aged 65 or older who had died at home between October 2002 and September 2004. The following information was collected: decedent characteristics, observed symptoms and end-of-life care provided during the last 48 hours of life. To assess the differences in characteristics and clinical course among decedents, the survey data were divided into two groups: cancer and non-cancer.

Results We evaluated 173 decedents with cancer and 61 decedents without cancer. The decedents with cancer were more likely to show symptoms of pain, acute confusion, or nausea/vomiting and less likely to display fever or cough than the decedents without cancer. In addition, decedents with cancer were more likely to receive intravenous drip injection or narcotic analgesia and less likely to be given heart massage, sputum suction, or antibiotics. After adjustment for age and other baseline characteristics, difference in the frequency of controlled pain remained significant.

Conclusions We observed that both the dying process and end-of-life care differed between elderly patients with cancer and those without. However, cancer itself is not an independent predictor of end-of-life symptoms or care.

Key words End-of-life care, Elderly, Cancer, Symptom, Home

Introduction

Due to the aging of the population and longer life spans, end-of-life care for the elderly has become a major national problem in Japan.[1,2]

Due to patients' preference for dying at home[1,3,4] and rising health care costs in Japan,[5] end-of-life care for the elderly at home has received much attention within the long-term care insurance system.[1]

The goal of palliative care is to achieve the best possible quality of life for patients and their families, in part by providing information on natural clinical courses and available treatment frameworks at home and by discussing care goals.[6,7] Therefore, primary sources of information are needed to assist physicians and nurses in discussing home end-of-life care programs with elderly patients and family members. Particu-

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

larly, the assessment and management of symptoms are central to high-quality end-of-life care, since dying patients frequently develop symptoms. As a number of researchers have suggested, we believe that the symptoms experienced by elderly patients with advanced cancer differ from those who do not have advanced cancer.[2,8] It is therefore logical to assume that end-of-life care for elderly patients should differ between those with and those without cancer. However, the prevalence of symptoms experienced and patterns of care received by elderly patients with or without cancer who are dying at home remain unclear.

The aim of this study was to assess and compare the frequency of symptoms and patterns of end-of-life care receipt between elderly patients with and those without cancer at home during the last two days of their lives. This study provides primary sources to assist medical teams, elderly patients and their families in designing home quality end-of-life care programs.

Methods

Study population

The Dying Elderly at Home (DEATH) project was a prospective study of elderly patients dying at home of an end-stage disease. It was conducted in collaboration with the nonprofit Japanese Society of Hospice and Home-care, which consists of general physicians and other medical and social professionals involved in hospice and home care. To recruit physicians for the study, we first selected the major members of the society who were clinical physicians and who were expe-

Table 1 Cancer and without cancer decedent characteristics and causes of death

Variable		Cancer (n=173)	Without cancer (n=61)	
		n (%)	n (%)	*P*
Sex	Female	75 (43.4)	37 (60.7)	0.02
Age (average±SD)		75.7±8.7	87.1±8.9	<0.01
ADL scale of disabled elderly	J=independent	5 (2.9)	3 (4.9)	0.01
	A=house-bound	15 (8.7)	4 (6.6)	
	B=chair-bound	40 (23.1)	8 (13.1)	
	C=bed-bound	90 (52.0)	45 (73.8)	
	Unknown	23 (13.3)	1 (1.6)	
Cognitive impairment	Present	50 (28.9)	44 (72.1)	<0.01
Major disease (primary tumor or noncancer disease)	Gastrointestinal	67 (38.7)	0	
	Gastric	42 (24.3)		
	Colorectal	25 (14.5)		
	Pulmonary	33 (19.1)	19 (31.1)	
	Liver	26 (15.0)	0	
	Pancreas	11 (6.4)	0	
	Prostate	7 (4.0)	0	
	Breast	4 (2.3)	0	<0.01
	Kidney	4 (2.3)	2 (3.3)	
	Uterine	3 (1.7)	0	
	Blood	3 (1.7)	1 (1.6)	
	Cerebrovascular	1 (0.6)	5 (8.2)	
	Cardiovascular	0	9 (14.8)	
	Others	9 (5.2)	21 (34.4)	
	Unknown	5 (2.9)	4 (6.6)	

ADL: activities of daily living

rienced in providing end-of-life home care. We then sent to these physicians a prospectus on our research. Sixteen clinic physicians agreed to participate, representing 16 clinics in Western Japan. The subjects of the study were 240 consecutive decedents aged 65 or older who had used the study clinics while diagnosed with any disease, including advanced cancer, and who had died at home between October 2002 and September 2004. Decedents were excluded if they were transferred to a hospital immediately before death because it is difficult to obtain information from a hospital. The following information was collected: sociodemographics; activities of daily living (ADLs) (Japan's Ministry of Welfare identifies four ranks of ADL in elderly people with disabilities[9]: Rank J (independence in ADLs), Rank A (house-bound), Rank B (chair-bound), and Rank C (bed-ridden)); cognitive impairment, observed symptoms; and end-of-life care provided during the last 48 hours of life. With the approval of the Japanese Society of Hospice and Home-care, we used a questionnaire that included a list of common end-of-life symptoms and treatments:

Symptoms

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

End-of-life care

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

Data collection

Immediately after the death of a study patient,

Table 2 Cancer and without cancer decedent symptom experience in last two days of life

Symptom	Cancer (n=173)	Without cancer (n=61)		Odds ratio*	95%CI
	n (%)	n (%)	*P*		
Dyspnea	79 (45.7)	26 (42.6)	0.68	0.55	0.11– 2.81
Pain (uncontrolled)	33 (19.1)	2 (3.3)	<0.01	0.82	0.06–10.61
Pain (controlled)	80 (46.2)	5 (8.2)	<0.01	10.73	1.76–65.25
Coma	77 (44.5)	20 (32.8)	0.11	2.09	0.46– 9.55
Acute confusion	44 (25.4)	3 (4.9)	<0.01	3.71	0.48–28.96
Anxiety	29 (16.8)	5 (8.2)	0.10	2.16	0.28–17.05
Dizziness	2 (1.2)	1 (1.6)	0.77	1.15	0.03–41.01
Nausea and Vomiting	49 (28.3)	5 (8.2)	<0.01	3.31	0.31–35.95
Anorexia	101 (58.4)	31 (50.8)	0.31	1.00	0.27– 3.75
Diarrhea	10 (5.8)	3 (4.9)	0.80	—	—
Constipation	12 (6.9)	4 (6.6)	0.92	1.89	0.15–23.64
Fever	41 (23.7)	26 (42.6)	<0.01	0.73	0.17– 3.18
Incontinence	31 (17.9)	6 (9.8)	0.14	5.39	0.90–32.18
Hematemesis	8 (4.6)	3 (4.9)	0.93	—	—
Hemoptysis	2 (1.2)	0 (0.0)	0.40	—	—
Bottom blood	11 (6.4)	5 (8.2)	0.62	—	—
Other hemorrhage	9 (5.2)	3 (4.9)	0.92	—	—
Cough	25 (14.5)	21 (34.4)	<0.01	0.57	0.11– 2.86
Sputum	51 (29.5)	23 (37.7)	0.23	0.92	0.20– 4.30
Other symptom	44 (25.4)	7 (11.5)	0.02	3.46	0.58–20.61

*: Controlling for age, sex, activities of daily living, cognitive impairment, and disease

the general practitioner (GP) who oversaw the patient was asked to fill out a questionnaire based on the patient's medical chart and on the physician's recollection of the clinical course. The GP also asked family members or visiting nurses who witnessed the last 48 hours of the patient's life to provide additional information.

The GPs and other information providers were blinded to the study hypothesis and to any anticipated study results. For ethical considerations, data on all eligible participants obtained from the Japanese Society of Hospice and Homecare remained anonymous.

The decedents were divided into two groups for analysis to confirm the differences in characteristics and clinical courses between subjects with cancer and those without. For each patient, the GP in charge recorded the disease as either cancer or noncancer. Data were collected on 173 decedents with cancer and 61 without cancer. The distribution of patients' characteristics is shown in Table 1. The research protocol was reviewed and approved by the Nagoya University Research Ethics Board.

Statistical analysis

The data were analyzed using Statview-J5.0. Group differences were compared using the unpaired-*t* test and the chi square test. We also performed multivariate logistic regression analysis to identify any independent association between cancer and symptoms or intervention, after adjusting for baseline characteristics. We present the results as odds ratios and 95% confidence intervals. A *P* value of less than 0.05 was considered statistically significant.

Results

As seen in Table 1, a significantly greater percentage of decedents with cancer were male compared to decedents without cancer. Those with cancer were also generally younger. On the whole, decedents with cancer scored lower in ADLs and in cognitive function. Among the primary sites of cancer, stomach was the most

Table 3 Cancer and without cancer decedent care receipt in last two days of life

Care	Cancer (n=173)	Without cancer (n=61)		Odds ratio*	95%CI
	n (%)	n (%)	*P*		
Heart massage	2 (1.2)	4 (6.6)	0.02	—	—
Intubation	0 (0.0)	0 (0.0)		—	—
Mechanical ventilation	0 (0.0)	1 (1.6)	0.09	—	—
Oxygen inhalation	63 (36.4)	19 (31.1)	0.46	0.98	0.23– 4.17
Airway placement	4 (2.3)	1 (1.6)	0.75	1.05	0.00–411.55
Sputum suction	41 (23.7)	23 (37.7)	0.03	0.41	0.09– 1.90
Hyperalimentation	17 (9.8)	1 (1.6)	0.04	3.42	0.22– 54.00
Antibiotics	20 (11.6)	17 (27.9)	<0.01	1.29	0.27– 6.21
Vasopressor	1 (0.6)	1 (1.6)	0.44	—	—
Blood transfusion	1 (0.6)	0 (0.0)		—	—
Intravenous drip injection	60 (34.7)	20 (32.8)	0.79	3.56	0.58– 21.94
Volume (average±SD)					
24–48 hours before death	467.2±306.8	705.9±397.6	<0.01	—	—
0–24 hours before death	360.8±299.0	666.7±343.0	<0.01	—	—
Opioids	82 (47.4)	0 (0.0)	<0.01	—	—
Urinary catheter placement	31 (17.9)	8 (13.1)	0.39	3.43	0.50– 23.61
Mental support	5 (2.9)	0 (0.0)	0.18	—	—
Religious healing	3 (1.7)	0 (0.0)	0.30	—	—
Others	11 (6.4)	2 (3.3)	0.37	1.21	0.02– 95.15

*: Controlling for age, sex, activities of daily living, cognitive impairment, and disease

prevalent (24.3%) followed by lung (19.1%), liver (15.0%), and colorectal area (14.5%). Pulmonary disease was the most prevalent (32.8%) disease among decedents without cancer.

Table 2 shows the decedents' symptoms during the last two days of their lives. Decedents with cancer were more likely to display controlled or uncontrolled pain, acute confusion, or nausea/vomiting and less likely to show fever or cough. However, after controlling for age, sex, ADLs, dementia, and disease, only controlled pain was determined to be a significant independent predictor, with an adjusted odds ratio of 10.73 (95% CI, 1.76–65.25).

Table 3 shows end-of-life care given to decedents during the last two days of their lives. Decedents with cancer were more likely to receive intravenous drip injection or narcotic analgesia and less likely to receive heart massage, sputum suction, or antibiotics. As for intravenous drip injection, decedents with cancer received smaller volumes than patients without cancer (467.2 ml vs 705.9 ml, respectively). After controlling for age, sex, ADLs, dementia, and disease, no factors were determined to be significant independent predictors.

Discussion

Consistent with some studies,[1,2,8] the present results revealed differences in end-of-life symptoms experienced and care received between elderly patients with cancer and those without it at home, where a growing percentage of elderly people spend their last years. However, after adjustment for age and other baseline characteristics, almost all of these differences in end-of-life symptoms and care received disappeared. Thus, our findings did not suggest that cancer itself is an independent predictor of end-of-life symptoms or care. The results add an end-of-life perspective to the current knowledge of end-of-life care at home, especially in Japan.

In our study, elderly decedents without cancer tended to be older and to have poorer physical and cognitive status than elderly decedents with cancer. Elderly patients, especially those without cancer, are more vulnerable to chronic medical problems, including dementia and stroke, and are less able to perform ADLs than are younger patients. Therefore, aged patients often die of nonspecific diseases as a result of old age.[1,2] The characteristics of decedents without cancer seem to reflect the situation of dying of old age. In addition, our results show that pulmonary disease was a common cause of death among patients who did not have cancer. This may be explained by the fact that aspiration pneumonia is prevalent among elderly patients dying of old age.[2,8]

Symptoms during the last two days

In our study, before adjustment, decedents with cancer and those without were reported to experience significant differences in the frequency of symptoms such as pain, acute confusion, nausea and vomiting, fever, and cough. After adjustment, differences in the frequency of controlled pain remained significant.

Our results suggest that pain control was a major problem for patients with cancer who were dying at home, compared to those without cancer who experienced pain only occasionally. There are several possible explanations for these findings. First, although it is generally believed that pain is less common in elderly decedents with cancer than in younger patients with cancer,[8,10] pain is prevalent in patients with end-stage cancer at home. Second, decedents without cancer were tolerant of pain because they were cognitively impaired[11] or older[12] compared to decedents with cancer. Third, patients without cancer could not inform nurses and physicians about their pain because of cognitive impairment or difficulty in communication.[11–13] It is possible that pain control is a major problem for dying community-dwelling elderly patients regardless of whether they have cancer or not. Thus, nurses and physicians should monitor and evaluate the pain of all patients on a daily basis, regardless of the presence or absence of cancer.

Surprisingly, acute confusion was not common in patients without cancer, unlike the case of patients with cancer. It was previously suggested that elderly patients with noncancer diseases, especially those with dementia, often show acute confusion.[8,14–16] Our results were inconsistent with this finding. Further research is needed to account for the difference in the prevalence of acute confusion between cancer and decedents without cancer at the end of life.

According to Griffie and Mckinnon,[17] nausea and vomiting affect 40 to 70% of patients with advanced cancer. Our results were consistent with this finding. Nausea and vomiting have com-

monly been associated with cancers of the gastrointestinal system.[17,18] The prevalence of gastric and colon cancer in primary sites may account for these symptoms. Additionally, the use of opioids is one of the most frequently identified causes of nausea and vomiting in persons with end-stage diseases.[17] Pain can also cause nausea and vomiting, and the higher prevalence of pain in patients with cancer contributes to the higher incidence of nausea and vomiting than in patients without cancer.[17]

Univariate analysis revealed that cough and fever were more prevalent in patients without cancer than in patients with cancer. Common causes of cough during end-stage disease include pulmonary disease such as pneumonia or lung cancer.[19] This may be due to the fact that a greater percentage of patients without cancer died of pulmonary disease (42.6%) than patients with cancer died of lung cancer (19.1%), as our results indicate. Although fever is not commonly reported among elderly patients,[20] our results suggest that, at the end of life, the management of fever is a major problem in elderly patients unless they have cancer.

End-of-life care during the last two days

As can be expected in the home setting, few decedents received life-sustaining interventions such as heart massage, intubation, or mechanical ventilation, regardless of whether they had cancer or not. Patients without cancer, however, were more likely to receive heart massage. This finding was consistent with previous studies.[21,22] There are two explanations for the difference. Because the process of dying of old age is not as clearly understood as that of cancer,[1,8] the GPs did not discuss end-of-life care plans with patients and their families. It is also possible that the concept of "end-of-life care for the elderly" was not properly understood by the study's physician.[2,23]

Decedents without cancer were more likely than those with cancer to receive sputum suction. Therefore, we can assume that some decedents with cancer displayed mild rather than severe sputum that did not need clearing. Morita et al.[10] and Andrews et al.[24] suggested that dehydration in patients with advanced cancer reduces sputum production and improves QOL. Dehydration may have resulted in reduced sputum among decedents with cancer. How to give drip infusions to elderly patients without cancer in the last days of their lives is an area that needs attention. As in a previous study in Japan,[25] the volume of drip infusion given to our decedents with cancer was approximately 500 ml/day. Our results added to the stock of information on the volume of end-of-life drip infusion in Japan.[26]

Hyperalimentation was more prevalent in decedents with cancer than in those without before multivariate adjustment. There are two possible explanations for this difference. As mentioned earlier, patients with cancer suffered from nausea and vomiting. As a result, general practitioners resorted to hyperalimentation to meet patients' nutritional needs. In addition, we hypothesize that a greater proportion of elderly decedents without cancer than with cancer received tube feeding instead of hyperalimentation; in Japan, elderly patients who cannot eat sufficiently are likely to receive tube feeding.[14,23] Further research is needed to determine the related factors accounting for the difference in referral patterns for hyperalimentation between decedents with cancer and those without.

Antibiotics were more prevalent in decedents without cancer before multivariate adjustment. We assume that the GPs gave antibiotics to patients without cancer who had a fever, because patients without cancer are generally more likely to experience fever than patients with cancer. However, among patients with dementia, there is insufficient evidence to support the positive effect of antibiotics on the prolongation of life[14,27,28]; their use also carries a risk of impaired renal function[27] and poorer cognitive function.[28] Therefore, because a greater percentage of decedents without cancer than those with cancer were cognitively impaired, it is not clear whether the use of antibiotics among decedents without cancer was appropriate.

The use of narcotic analgesics was more prevalent in decedents with cancer than in those without. Because patients with cancer were more likely to experience pain than those without cancer, the results do not seem surprising. However, we may also speculate that pain was not well controlled in decedents with cancer even though narcotic analgesics were frequently used. Conversely, none of the decedents without cancer received a narcotic analgesic. Because few patients without cancer complained of pain, it is natural that the GPs refrained from giving them narcotic analgesics. However, in our study, nearly half of

the patients without cancer presented with dyspnea. Because opioids can alleviate dyspnea,[8,29] it is possible that the GPs did not properly understand the use of opioids for dyspnea.

Study limitations

There were several important limitations to this study. First, this study partly relied on family members' accounts of patient symptoms, because the settings were the communities. This may have biased the researchers' evaluation. Second, the results must be interpreted with caution since we lack information about the degree of symptoms experienced. Therefore, we cannot thoroughly evaluate whether or not the symptoms were properly managed. In addition, because the duration of the home end-of-life care could contribute to the use of intervention, the lack of information about the duration weakened the power of our results concerning the differences in end-of-life intervention. Third, we enlisted each clinic to perform evaluations because of the large number of settings. This may have biased the researchers' evaluations and limited the validity of the results, since it is possible that the data-collection procedures and quality varied depending on the GPs in charge of data collection. Fourth, due to the difficulty of collecting data, we excluded patients who received home care but were finally admitted to hospital just before death. We believe that such patients, if they have serious symptoms, are an interesting target population. Finally, the small number of patients and limited variety of study settings also limited generalization. In addition, as mentioned above, the Japanese Society of Hospice and Home-care is interested in hospice and home care, and thus selection bias is also possible. Larger studies in other areas of research may help further reveal the current situation of end-of-life care at home in Japan.

Conclusion

We investigated the differences in symptom experience and end-of-life care between elderly patients with or without cancer who were dying at home in Japan. Our results suggested that both the dying process and end-of-life care differed between elderly patients with cancer and those without. However, cancer itself is not an independent predictor of end-of-life symptoms or care. Larger studies are needed to substantiate our findings.

Acknowledgements

This study was supported by the Ministry of Health, Labour and Welfare of Japan. We extend our appreciation to all members of the Japanese Society of Hospice and Home-care, especially Mr. Nobuyoshi Daito and Mr. Sunchi Ryan. We also thank the following research assistants: Ms. Noriko Sano and Mr. Minoru Nishi.

References

1. Hashimoto H. Establishment of terminal care systems on the basis of patients' will. In: Iryokeizaikikou ed. Iryohakusyo. Tokyo: Nihon Iryokikaku; 2001:47–58. (in Japanese)
2. Suzuki Y, Iguchi A. Geriatric comprehensive medicine: an approach to terminal care. J Jpn Med Assoc. 2004;93:2508–2513. (in Japanese)
3. Sauvaget C, Tsuji I, Li JH, et al. Factors affecting death at home in Japan. Tohoku J Exp Med. 1996;180:87–98.
4. Tilden VP, Drach LL, Tolle SW. Complementary and alternative therapy use at end-of-life in community settings. J Altern Complement Med. 2000;8:897–906.
5. Hiroi Y. Future prospects of hospice and palliative care from a medical economics point of view. Taminaru Kea. 1998;8(Suppl): 6–11. (in Japanese)
6. Morrison RS. Survival in end-stage dementia following acute disease. JAMA. 2000;284:47–52.
7. Pekmezaris R, Breuer L, Zaballero A, et al. Predictors of site of death of end-of-life patients: the importance of specificity in advance directives. J Palliat Med. 2004;7:9–17.
8. Uemura K. Characteristics of end-of-life care for the elderly. In: Iguchi A ed. Future Gerontology. Nagoya: Nagoya Daigaku Shuppan Kai; 2000:302–305. (in Japanese)
9. Hirakawa Y, Masuda Y, Kimata T, Uemura K, Kuzuya M, Iguchi A. Effects of home massage-rehabilitation therapy for the bedridden elderly: a pilot trial with a three-month follow-up. Clin Rehabil. 2004;18:1–8.
10. Morita T, Tsunoda J, Inoue S, Chihara S, Ichiki, T. Symptom prevalence and risk factors in terminally ill cancer patients. Jpn J Cancer Clin. 1998;44:879–884. (in Japanese)
11. Porter FL, Malhotra KM, Wolf CM, et al. Dementia and response to pain in the elderly. Pain. 1996;68:413–421.
12. Tilden VP, Tolle SW, Drach LL, Perrin NA. Out-of-hospital death: advance care planning, decedent symptoms, and caregiver burden. J Am Geriatr Soc. 2004;52:532–539.
13. Shuster JL. Palliative care for advanced dementia. Clin Geriatr Med. 2000;16:373–386.
14. Hirakawa Y, Masuda Y, Kimata T, Uemura K, Kuzuya M, Iguchi A. Terminal care for elderly with dementia in two long-term care hospitals. Nippon Ronen Igakkai Zasshi. 2004;41:99–104. (in Japanese)
15. Kuebler KK, Heidrich DE. Delirium/acute confusion. In: Kuebler KK, Berry PH, Heidrich DE ed. End-of-Life Care—Clinical Practice Guidelines. Philadelphia: WB Saunders; 2002:253–267.
16. Bedford S, Melzer D, Guralnik J. Problem behavior in the last

year of life: prevalence, risks, and care receipt in older Americans. J Am Geriatr Soc. 2001;49:590–595.
17. Griffie J, Mckinnon S. Nausea and vomiting. In: Kuebler KK, Berry PH, Heidrich DE ed. End-of-Life Care—Clinical Practice Guidelines. Philadelphia: WB Saunders; 2002:333–343.
18. Mercadante S, Casuccio A, Fulfaro F. The course of symptom frequency and intensity in advanced cancer patients followed at home. J Pain Symptom Manage. 2000;20:104–112.
19. Berry PH. Cough. In: Kuebler KK, Berry PH, Heidrich DE ed. End-of-Life Care. Philadelphia: WB Saunders; 2002:235–241.
20. Kuzuya M. Characteristics of age-related illnesses. In: Iguchi A ed. Future Gerontology. Nagoya: Nagoya Daigaku Shuppan Kai; 2000:51–56. (in Japanese)
21. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. J Am Geriatr Soc. 2000;48:S146–S153.
22. Lynn J, Teno JM, Phillips RS, et al. For the SUPPORT investigation. Perceptions by family members of the dying experience of older and seriously ill patients. Ann Intern Med. 1997;126: 97–106.
23. Murai A. Terminal care for the elderly. Nippon Ronen Igakkai Zasshi. 1999;36:623–626. (in Japanese)
24. Andrews M, Bell ER, Smith SA, et al. Dehydration in terminally ill patients. Is it appropriate palliative care? Post Grad Med. 1993;93:201–208.
25. Morita T, Tsunoda J, Inoue S, Chihara S. Characteristics of palliative care for elderly cancer patients—a pilot study at our hospital. Geriatr Med. 1997;35:1505–1511. (in Japanese)
26. Morita T, Shima Y, Adachi I. Attitudes of Japanese physicians toward terminal dehydration: a nationwide survey. J Clin Oncol. 2002;20:4699–4704.
27. Evers MM, Dushyant P, Daniel P, Khalid K, Marin DB. Palliative and aggressive end-of-life care for patients with dementia. Psychiatr Serv. 2002;53:609–613.
28. Shuster JL. Palliative care for advanced dementia. Clin Geriatr Med. 2000;16:373–386.
29. Kuebler KK. Dyspnea. In: Kuebler KK, Berry PH, Heidrich DE ed. End-of-Life Care—Clinical Practice Guidelines. Philadelphia: WB Saunders; 2002:301–315.

Review Article

Aid Coordination Mechanisms for Reconstructing the Health Sector of Post-Conflict Countries

JMAJ 49(7・8): 251–259, 2006

Hidechika Akashi,[*1] Noriko Fujita,[*1] Rumiko Kakishima Akashi[*2]

Abstract

Some trends have been observed in international assistance for the reconstruction of the health sector in countries that have suffered a conflict throughout their entire country. The authors, having pursued aid activities in Cambodia and Afghanistan and reviewed past experiences, propose useful aid coordination mechanisms for post-conflict countries. The mechanisms include the establishment of a national coordination group between the recipient country's Ministry of Health, donors and NGOs, sub-coordinating groups for specific technical topics, and coordination groups at the provincial level. Additionally, the involvement of NGOs, such as umbrella NGOs, is indispensable to the reconstruction process. Although aid work sharing and the participation of military forces in reconstruction activities may be necessary under certain circumstances, we still need to examine strategies to include them. Consequently, it is time for the international community to integrate aid activities for post-conflict countries in order to respond immediately and effectively to their immediate needs.

Key words Post-conflict, Afghanistan, Cambodia, Aid coordination, Health

Introduction

The past several decades have been characterized by a series of conflicts around the world as witnessed in the countries such as Cambodia, Kosovo, East Timor, and Afghanistan. Obviously, the violence resulting from conflicts increases morbidity, mortality and disabilities.[1] Conflicts are most likely to destroy a country's health system or undermine the quality and availability of public health care owing to paralysis in decision-making, budgetary deficits, and low morale among government workers.[2] Rebuilding the health care system is not an easy task,[3] especially in post-conflict countries where the entire country has been devastated, such as Cambodia and Afghanistan. Immediate and coordinated international support expedites the reconstruction process.

The increase in conflicts since the 1950s has increased opportunities to assist afflicted countries.[4] As Launtze and her colleagues[5] point out, internal and external organizations (such as civil society organizations, UN agencies, donors, non-governmental organizations, and international organizations) have been criticized for recurring difficulties in coordinating such activities. The international aid community, therefore, needs to learn from its experiences, formulate concrete aid strategies on coordination for post-conflict countries, and establish an international system for providing guidance and technical and policy advice to fledging governments emerging from conflict.[6] Kreczko[7] extracted elements from experiences in Afghanistan to propose an aid framework for how international donors should provide humanitarian assistance to post-conflict countries facing complex emergencies. However, his framework did not include the necessary

*1 Expert Service Division, Bureau of International Cooperation, International Medical Center of Japan, Tokyo
*2 Ph.D. Program, Columbia University, School of Social Work, New York, USA
Correspondence to: Hidechika Akashi MD, PhD, MPH, DTMH, Department of International Health, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
Tel: 81-52-744-2109, Fax: 81-52-744-2114, E-mail: akashih@med.nagoya-u.ac.jp

specific mechanisms for implementing activities in the field.

There are some potential difficulties with coordination, including, 1) how to create ownership by the Ministry of Health (MOH) and to develop the capacity of the MOH, 2) how to communicate national policy to the peripheral level, 3) how to coordinate donors and external experts, and provide advice from external actors to the MOH, 4) how to include NGOs in policy making, how to develop the capacity of local NGOs, and how to coordinate with NGOs, and 5) how to coordinate humanitarian activities with other actors, such as military forces.

The authors of this paper have pursued health reconstruction efforts in Cambodia and Afghanistan and witnessed some trends in health aid. Based on our involvement in health assistance and a review of earlier reports in other post-conflict countries including Rwanda, Uganda, Somalia, East-Timor, and Kosovo as well as Cambodia and Afghanistan, this paper describes the type of coordination activities and mechanisms required from the international aid community in post-conflict countries, and examines: 1) the participation of national and local governments, 2) the MOH and donor coordination, 3) NGO involvement, 4) the involvement of other actors.

Table 1 summarizes reports on the seven countries covering coordination groups, membership of the coordination group, issues, lessons, and recommendations. From these experiences, we tried to extract meaningful common mechanisms for better coordination. In addition, we tried to identify useful approaches from the lessons learnt and recommendations received from different countries, although some of the details were unclear due to deficiencies in the reports.

Experiences

Health coordination groups—Coordination mechanisms between the government and donor agencies

Over the past several decades, the number of actors involved in the reconstruction of post-conflict countries and their collaborative efforts have increased.[8] Our review shows that some coordination efforts were implemented in many post-conflict countries, However, the methodology is neither clear and nor established yet, and there is still a trend for individual actors to initiate their own activities and for coordination not to always occur immediately.

Coordination groups at national level

In many countries there is a coordination group at the national level, and NGOs usually participate in this group. However, the Ministry of Health (MOH) is neither always included, nor strengthened. In Uganda in the 1980s, the Health Policy Review Commission was formulated to coordinate actions among the recipient country and donors. However, it served to present financial aid for the programs of expertise and the interests of donors and failed to seek to enhance the policy-making capacity of the Ugandan MOH.[9] In the case of Rwanda,[10] the UN Rwanda Emergency Office (UNREO) was set up before the establishment of the new transitional government, and its roles were preparing and elaborating discussion and policy papers, overall information collection, supporting UN agency operation, and assuming the role of secretariat for the donor meetings. After the establishment of the new transitional government, UNICEF initially concentrated on supporting the new government to re-establish functioning ministries, and it expected that the government, rather than UN agencies, could play its coordination role. However, technical coordination was outside of mandate of UN field coordination capacity, and UNREO's ability to provide authoritative leadership and effective management coordination was limited. Instead, two largest donors within the international communities led initiatives. Consequently, the technical coordination mechanism was unclear, and Rwandan ownership was not promoted.[10]

Even in the countries that have no MOH, efforts to involve local representatives from the different factions can be tried to foster the ownership of the recipient countries. In Kosovo,[11] limited local ownership was observed in the initial policy formulation process for "Interim Health Policy Guidelines". In this process, newly formed health policy-working group appointed by Department of Health and Social Welfare of UN Mission in Kosovo (UNIMIK) was involved, however, the weakness of ownership was recognized by WHO and UNIMIK, and some representatives from the different factions were added into this health policy-working group. In Somalia,[4] a mechanism for aid coordination was

Table 1 Coordination mechanisms in different post-conflict countries

Country (Year of events/ start of support)	Coordination group (CG)	Membership of CG and their role	Issues/Features	Lessons/Recommendations
Uganda (1987)	Yes (Health Policy Review Commission)	Expatriate technical advisors working with MOH, including NGOs	• Little enhancement of policy making capacity at government level. • Donors tended to support their own interests. • There was no national health framework. • Training of MOH staff was limited.	
Cambodia (1992)	Yes (CoCom: Coordination Committee at national level, ProCoCom: Provincial Coordination Committee at provincial level)	Members: MOH & external donors, NGOs (national & international) Chaired by MOH Role: • monitoring and evaluating all heath activities • advising MOH • making recommendations to MOH	• An umbrella NGO (MEDICAM) existed, with a seat in CoCom. • Introduction of subcontracting to NGOs.	UNTAC worked according to the three key principles of sovereignty, respect for local capacity, and balance of assistance for all areas.
Rwanda (1994)	Yes (UNREO: UN Rwanda Emergency Office)	UN agencies Role: • preparing policy papers • collectioning + disseminationing information • supporting UN agencies • acting as secretariat for the Disaster Management Team, NGO, and donors	• Technical coordination was incomplete. • Responsibility for technical coordination lay outside UNREO's mandate. • UNICEF, WHO etc. maintained responsibility for technical coordination individually. • Authority of coordination by UNREO was unclear. • Two largest donors made initiatives. • UNICEF initially concentrated on supporting the new government.	The government should play a coordinating role.
Somalia (1994)	Yes (linked with UNOSOM: UN Operation in Somalia)	External donors, UN agencies, NGOs, and Somali factions		Withdrawal of UN forces due to bad security
East-Timor (1999)	Different form (INTERFET →UNTAET→Interim health authority) because of no existing government	UN and International NGOs	• Local NGOs were not included in UNTAET. • Umbrella NGO, East-Timor NGO Forum was formulated. • Utilization of Local NGOs in sub-contracting and training roles was conducted through Community Empowerment Program	The lack of involvement of local NGOs was criticized as a new form of colonialism.
Kosovo (1999)	Yes (health policy working group)	Policy working group composed of Kosovo Albanians, with technical assistance from WHO Consultative meeting with local/ international medical communities	• Interim health policy guidelines were established. • Policy working group was appointed by the Department of Health and Social Welfare for making ownership (but, Serbian medical community was not successfully included).	• The roles of various key actors should be defined early. • WHO can play the lead role in health policy development. • The lead policy organization should concentrate on policy development and coordination, and support the process of its implementation.
Afghanistan (2001)	Yes (Local CGHN: Local Consultative Group for Health and Nutrition at national level, PCC: Provincial Coordinating Committee at provincial level	Members: MOH & external donors, NGOs (national & international) Chaired by MOH Role: • monitoring and evaluating all heath activities • advising to MOH • making recommendations to MOH	• There is no umbrella NGO, however, there is an informal voluntary network. • Subcontracting to NGOs to run provinces and districts was widely introduced. • Donors and NGOs who support specific activities (such as nursing school) have responsibilities for specific sectoral and geographic areas. • Military forces participate in health development activities	

Table 2 Topics of sub-coodination meetings

	Cambodia	Afghanistan
Personnel	Human resources	Human resources
Maternal and child health	MCH	Women's health (SMI/Reproductive health) Child health Nutrition EPI
Other	Health economics Mental health Oral health Prevention of blindness Surgical training Medical technology Laboratory Medical ethics and research	Salary and incentive standardization for NGOs Essential drugs and private sector Health management information system Hospital management Community based health care IEC HIV/AIDS Communicable disease and emergency response
Total	10 topics	13 topics

established, which was linked with UNOSOM (UN Operation in Somalia) as an independent unit, to build legitimacy both nationally and internationally through an ongoing process of dialogue with the different Somali factions, international donors, UN agencies, and NGOs. However, it was ended due to the subsequent breakdown in the security situation and the withdrawal of UN forces.

In Cambodia and Afghanistan, on the other hand, the Ministry of Health has had a strong coordinating role, and has established effective partnerships with UN agencies, donors, and academic institutions.[6,12] In addition, the MOH allocated major donors to key underserved rural areas, and used major NGOs to deliver primary health care packages in Afghanistan.[6]

The Coordination Committee (CoCom: this name was subsequently changed to Technical Working Group for Health.) in Cambodia and the Local Consultative Group for Health and Nutrition in Afghanistan[13] as a coordination group at national level, progressed with the ownership of the two countries respectively. The major advantages in the case of both countries were that the representatives of the MOH chaired the group and were the major actors in decision-making, and that donors played the role of advisors to the MOH.

A coordination group at the national level should function to support policy-making that encourages the active participation of a recipient country in the process, and strengthens the capacity of its MOH. Such a national coordination group will enhance the ownership and initiatives of a recipient government in the reconstruction process.

Sub-coordination groups under the national coordination groups for technical issues

A national coordination group often faces difficulties in dealing with specific health issues, and its members are not always familiar with all technical issues. Thus, sub-coordination groups under the national coordination groups in which the MOH technical staff and aid agency advisors attend, can be useful for discussing specific health policies and submitting technical reports or recommendations to the national coordination group. Smaller-scale working groups under sub-coordination groups may also be effective for discussing further detailed issues and topics.

There are few descriptions of these coordination groups held under the national coordination group. However, the Sub-CoComs in Cambodia[12,14] and the Task Forces and Working Groups in Afghanistan operating under the national coordination group which we observed, were formulated to perform these functions (see Table 2 for topics discussed at these groups).

One matter that should be noted is that topics to be discussed at the sub-coordination groups should be selected based on the needs of a recipient country and not based on the political will of donors, as this may weaken donor coordination.

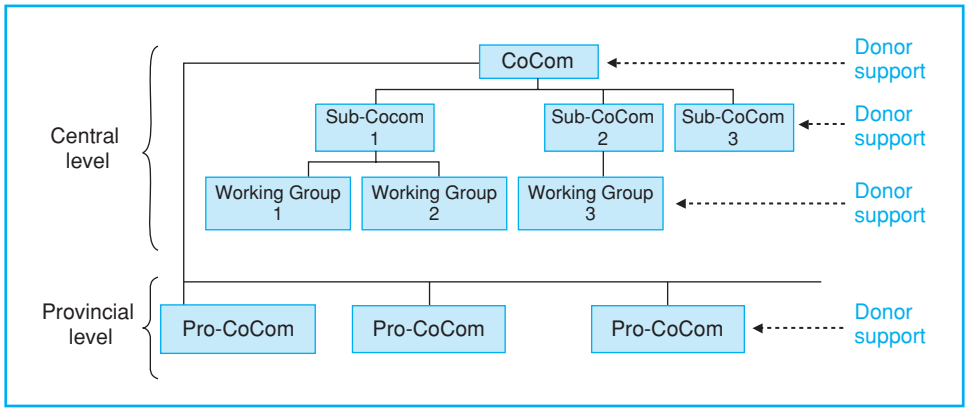

Fig. 1 Aid coordination mechanisms in Cambodia

We observed one case in which a donor tried to establish a working group which would discuss almost the same topics as other groups, in order to seize the political initiative in that field.

Coordination groups at provincial level

Coordination at the provincial level has also been little reported on, except in Cambodia and Afghanistan. In Cambodia, the Provincial Coordination Committees (Pro-CoCom; this name was also changed to Provincial Technical Working Group for Health) were established to support the local governments' implementation of national policies, and advisors from UNICEF and WHO worked with provincial health departments under this scheme (see Fig. 1 for the coordination mechanism in Cambodia). In Afghanistan, the process is underway to establish Provincial Coordinating Committees (PCC). Such collaborative arrangements are effective for coordinating donor support of health reconstruction at the provincial level.

Humanitarian agencies in countries such as Kosovo, Afghanistan, and Iraq are increasingly facing the need to work closely with, and even be coordinated by and support the capacity of, national government or quasi-state entities.[6] Our review of initiatives in some post-conflict countries indicates that coordination mechanisms at the national and provincial levels are indispensable in rebuilding the health sector.

Involvement of NGOs

NGOs have been important actors in reconstructing the health sector of post-conflict countries, and three types of participation mechanisms have been notable in providing assistance. Considering their advantages, the international aid community must include NGO participation as a component of future aid strategy.

Involvement of NGO in coordination groups

To benefit most from the collaboration of NGOs, the recipient government, and donors, a specific mechanism is required. The mechanism needs to function to convey the opinions of NGOs to the MOH and the aid community as well as the national policies and other relevant information to NGOs. The first type of mechanism is for the NGOs to have some seats in coordination groups at the national level and also at the provincial level.

In many countries that we reviewed, NGOs had opportunities to participate in national coordination groups, sometimes individually, and sometimes as representatives of an umbrella NGO. At the same time, it is important that local NGOs should not be neglected. For instance, the involvement of only international NGOs was criticized as a new form of colonialism in East Timor, when local NGOs were not included in the national coordination groups.[15,16] In this way, NGOs' views can be reflected in health policies, and the policies can be implemented at the grass-roots level.

Umbrella NGO

The second mechanism is an umbrella NGO or NGO network in post-conflict health reconstruction efforts which can support the above functions.

In the case of Cambodia, an umbrella organization, MEDICAM, which coordinates various

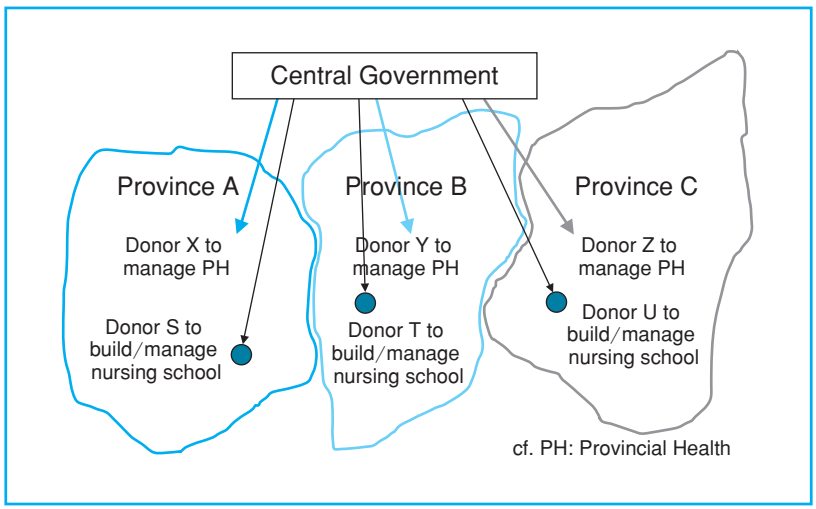

Fig. 2 Tasks subcontracted to donor agencies in Afghanistan

health NGOs, was created, and its representative received an official seat in CoCom.[14] MEDICAM has performed the functions described above, and through this organization, the MOH and donors have been able to gain knowledge about NGO activities. In East Timor, the East Timor NGO Forum was formed as a local NGO umbrella body, reflecting a desire to shift donors' priorities and seeking to realize the vision of local NGOs playing a necessary role in the process of democratization.[15] In Afghanistan, a formal umbrella NGO has not been established, although there has been an active voluntary network of NGOs, and several major NGOs involved in this network have participated in Local Consultative Groups.

Subcontracting NGOs

The third type of mechanism is subcontracting to NGOs. As Loevinsohn and Harding have noted,[17] this type of work sharing may be especially useful in countries, whose health service system has been devastated and whose public health administration capacity is at a minimum, due to factors such as a shortage of health personnel and decimated health facilities as a result of a conflict.

This type of mechanism was observed in Cambodia, East Timor, Afghanistan and other countries.[17] In Cambodia, some NGO subcontracting was attempted in running local governments, national health facilities, and programs. In Afghanistan, the Performance-based Partnership Agreement (PPA) was drawn up as a way of subcontracting to NGOs. In addition, the NGOs and donors in charge of supporting specific institutions in Afghanistan, such as nursing schools in specific areas, were selected and subcontracted (Fig. 2).

Some problems have been observed, however, with regard to subcontracting to NGOs. The first is ownership. Humanitarian agencies are increasingly being forced to work where no legitimate government exists, resulting in the increasing independence of agencies from local authorities.[6] The second issue is related to brain drain. In one example in Cambodia, some local NGOs, with financial support from a donor, hired skilled MOH personnel, and consequently government services deteriorated due to a drain of the necessary resources to the NGOs. In a subcontracting process, care must be taken to ensure that subcontracted NGOs will not obstruct the empowerment of the recipient government. A third issue is the sustainability of local health administration. Local and international NGOs in Cambodia and Afghanistan, with funding from donors, have played a primary role in health service provision on behalf of the local governments. However, some or all of their activities may need to be handed over to the local government when funding ends. Thus, in consolidating an aid strategy for post-conflict countries, there is a need to develop a clear plan of how the withdrawal of donor funding and the transfer

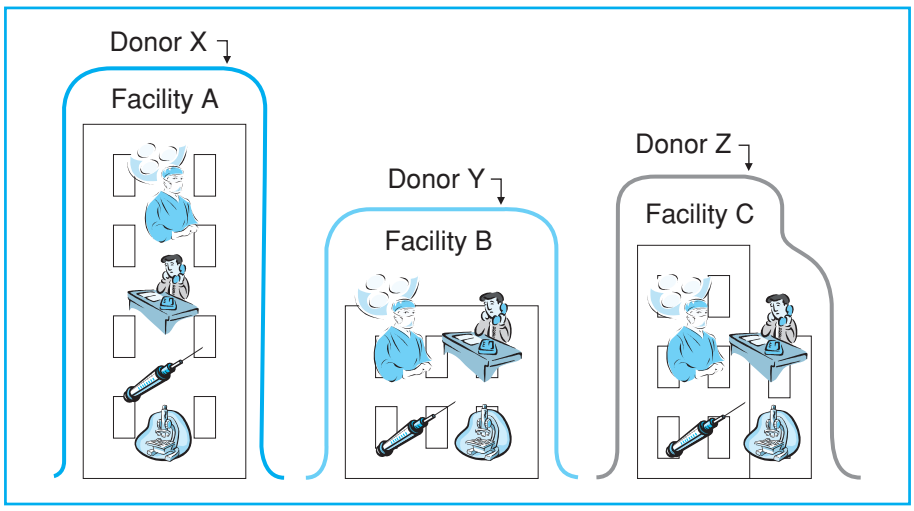

Fig. 3-1 Sharing aid work by facility (former way of conducting aid prousior)

of NGO activities to the local governments, in addition to the empowerment of the local governments, should be achieved.

In evaluating the effectiveness of NGO subcontracting, therefore, it is necessary to assess the contribution of NGOs not only in improving health indicators in their field of responsibility but also in strengthening the capacity of local public health institutions,[18] as well as national health systems. The capacity building of a recipient country's public health sector must be prioritized in aid efforts. Without an empowered public sector, the health system will neither be developed nor sustained when international post-conflict assistance terminates.

Other aid coordination trends and issues

As discussed above, many new attempts have been implemented to assist post-conflict countries. In Afghanistan, two additional forms of activities have been observed and they have indicated important issues for donors in formulating an effective health aid strategy for post-conflict countries.

Stratification of aid

In Cambodia, each donor agency usually provided a comprehensive aid package to health facilities that included the reconstruction of buildings, the provision of equipment, and the training of local human resources (Fig. 3-1). However, in Afghanistan, donor aid was rather more stratified, with each donor supporting an aspect of assistance, resulting in multiple donors performing their own aid activities and contributing to a joint health aid package for a health facility. For example, one aid organization renovated hospitals or health centers, while other agencies provided equipment, and others trained their staff. In this way, one health facility was supported by various aid agencies (Fig. 3-2). This stratification of aid activities, or aid work sharing, may have been due to the limited capacity of each donor or the restricted scope of aid schemes.

However, the stratification of aid creates some problems. One of the side effects of stratification is that aid agencies, especially bilateral donors, often face difficulties in generating domestic political visibility in supporting a particular health organization[19] and may become reluctant to provide assistance. It can also cause imbalanced aid. For instance, some facilities received assistance for building reconstruction but for neither equipment nor training.

To avoid this imbalance, in Afghanistan, some donor agencies assisted building renovation only when equipment was made available by other donors. To implement aid stratification more efficiently, a coordination model was formulated in the field of nursing education as a joint project by various agencies. One NGO that is assisting a nursing school in Kabul and Japanese-side as a donor agency agreed on a collaborative effort and generated an aid stratification format

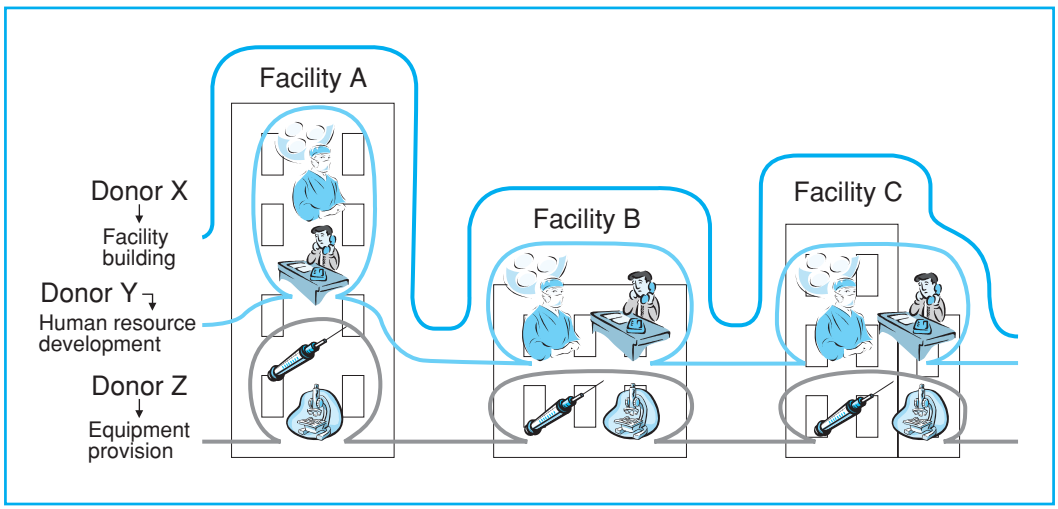

Fig. 3-2 Stratification of aid (Sharing aid work by task)

whereby the NGO would train nurses, the donor agency would renovate facilities and provide equipment and some budgetary support, and another selected local NGO would support the management of the nursing school (HIS; Institute of Health Science) in one province. The MOH approved this work sharing format and intends to replicate it in eight nursing schools. The effectiveness of this format model needs to be examined. Once its benefit has been verified, it should be included in aid mechanisms so that the model can be replicated as an aid stratification strategy in other post-conflict countries.

The participation of military forces in aid activities

Another feature of aid to Afghanistan is that military forces have participated in aid activities. The participation of military forces in aid activities is not new, and has been observed in a series of recent emergencies in Afghanistan, Somalia, the Balkans, and Iraq. Previously the role of military forces was mainly to maintain order. However, the U.S. military forces and the International Security Assistance Force (ISAF) in Afghanistan have served not only to help maintain order but also to reconstruct health related-facilities such as hospitals and medical schools.[20]

Furthermore, many American-led civil and military provincial reconstruction teams are working to rebuild hospitals and schools, provide drugs and equipment, and even deliver clinical services, and medical specialists of the U.S. military forces have been conducting clinical training in Afghanistan as well.[6] Actually, the main obstacle to reconstruction programmes is the security situation.[21] Especially in the early stage of reconstruction efforts, aid activities tended to concentrate on the capital and surrounding areas owing to poor security in rural areas.[9] This tendency was also observed in Cambodia, and the reconstruction process was delayed in rural areas as well. Therefore, the deployment of military assistance may be effective for the speedier reconstruction of rural areas.

However, the direct participation of military forces in the health sector makes it difficult to distinguish aid organizations from armed forces, and aid workers can be more easily targeted by anti-government forces.[21,22] Recent events actually show that foreigners, including international aid workers, are being targeted by anti-government fighters.[23] In addition, some NGOs are not in favor of military participation in humanitarian activities and have even rejected participation in aid activities conducted under the supervision of peacekeeping authorities.[24] The participation of armed forces is therefore a controversial issue. The international community should clarify the role of military forces in humanitarian assistance and endeavor to promote an environment in which aid agencies do not have to be restricted in their activities for security reasons.

Conclusion

Aid agencies have accumulated experience in reconstruction of the health sector in post-conflict countries. What we need for future health assistance is not individual action by different donors but coordinated action by the international aid community. It is time for the international aid community to evaluate aid in the light of the trends and activities identified above, and agree upon a strategy of integrating individual competencies into coordinated assistance mechanisms, in addition to a broad framework. We suggest development of coordination mechanisms, as one method to help post-conflict countries rebuild their health sector. NGOs, including local NGOs, should be involved in this process. Although some issues still remain, we believe that such a consensus will allow a quicker, more effective and systematic response to the rebuilding of war-torn countries, and that these coordination mechanisms can be useful to other developing countries.

Acknowledgements

This research was supported by the International Cooperation Research Grant for the "Study on strengthening social development approach on health and district health system in developing countries" from the Ministry of Health, Labor and Welfare.

References

1. Zwi A, Ugalde A. Political violence in the third world: a public health issue. Health Policy and Planning. 1991;6(3):203–217.
2. Ugalde A, Selva-Sutter E, Castillo C, et al. The health costs of war: can they be measured? Lessons from El Salvador. BMJ. 2000;321:169–172.
3. Richards T. Afghanistan struggles to build post-conflict health care. BMJ. 2003;326:837.
4. Macrae J, Zwi A, Forsythe V. Aid policy in transition: a preliminary analysis of 'post'-conflict rehabilitation of the health sector. Journal of International Development. 1995;7(4):669–684.
5. Launtze S, Leaning J, Raven-Roberts A, Kent R, Mazurana D. Assistance, protection, and governance networks in complex emergencies. Lancet. 2004;364:2134–2141.
6. Salama P, Spiegel P, Talley L, Waldman R. Lessons learned from complex emergencies over past decade. Lancet. 2004; 364:1801–1813.
7. Kreczko A. The Afghan experiment: the Afghan support group, principled common programming and the strategic framework. Disasters. 2003;27(3):239–258.
8. US Mission to the UN. Global humanitarian emergencies, 1998. New York: United Nations; 1998.
9. Macrae J, Zwi AB, Gilson L. A triple burden for health sector reform: 'post'-conflict rehabilitation in Uganda. Social Science and Medicine 1996;42(7):1095–1108.
10. Borton J. An account of co-ordination mechanisms for humanitarian assistance during the international response to the 1994 crisis in Rwanda. Disaster 1996;20(4):305–323.
11. Shuey DA, Qosaj FA, Shouten EJ, et al. Planning for health sector reform in post-conflict situations: Kosovo 1999–2000. Health Policy. 2003;63:299–310.
12. Lanjouw S, Macrae J, Zwi AB. Rehabilitating health services in Cambodia: the challenge of coordination in chronic political emergencies. Health Policy and Planning. 1999;14(3):229–242.
13. Ministry of Health. Consultative group for health and nutrition, Terms of reference. Kabul: Ministry of Health, Islamic Transitional Government of Afghanistan; 2003.
14. Akashi H. Improvement of Health Care. The Kingdom of Cambodia. —From reconstruction to sustainable development—. Tokyo: Institute for International Cooperation, Japan International Cooperation Agency; 2002.
15. Patrick I. East Timor emerging conflict: the role of local NGOs and international assistance. Disaster. 2001;25:48–66.
16. Povey G, Mercer MA. East Timor in transition: health and health care. International Journal of Health Services. 2002;32 (3):607–623.
17. Loevinsohn B, Harding A. Buying results? Contracting for health service delivery in developing countries. Lancet. 2005;366: 676–681.
18. Putoto G. The role of northern NGOs in rehabilitating the health sector in post-conflict settings: a need for a critical analysis. World Hospitals and Health Services. 1997;33(2):17–21.
19. Editorial. Afghanistan's health challenge. Lancet. 2003;362:841.
20. Kuehn BM. A long road: Army veterinarians provide humanitarian aid, rebuild infrastructure in Iraq and Afghanistan. Journal of the American Veterinary Medical Association. 2004;224:176–176,190.
21. Ahmad K. Warlords and bandits slow Afghanistan's efforts to rebuild. Attacks drive relief workers from some areas. Lancet. 2003;362:710–711.
22. Bruderlein C, Leaning J. New challenges for humanitarian protection. BMJ 1999;319: 430–435.
23. Turone F. Preparing for the worst. BMJ. 2003;326(7383):244.
24. Weissman F. Humanitarian action and military intervention: temptations and possibilities. Disasters. 2004;28(2):205–215.

Review Article

Ocular Manifestations in Behçet's Disease

JMAJ 49(7・8): 260–268, 2006

Takahiko Hayashi,*1 Nobuhisa Mizuki*1

Abstract

Behçet's disease is a refractory inflammatory disease; its cause is unknown and it presents with repeated acute inflammation in various organs throughout the body. Its 4 major manifestations are oral aphthae, ocular manifestations, skin manifestations, and genital ulcers. Frequently appearing in the mongoloid population in the vicinity of the Silk Road, the disease is rare in Europeans and Americans. There are currently no laboratory findings useful in and specific to the diagnosis of Behçet's disease. Behçet's disease is diagnosed based on a combination of clinical manifestations. In Japan, the diagnostic criteria have major and minor manifestations and the disease is classified as a complete, incomplete, possible, or specific type based on the combination of those manifestations. This review discusses the clinical manifestations of Behçet's disease with a focus on ocular manifestations.

Key words Behçet's disease, HLA-B51, Uveitis, Vasculitis

Introduction

Behçet's disease was first described by Professor Hulusi Behçet, a Turkish dermatologist, in 1937,[1] but an ailment akin to Behçet's disease had previously been described by the noted Greek physician Hippocrates in the 5th century BC. The history of this disease is extremely old, but it was first systematically described by Professor Behçet in the 20th century.

Behçet's disease is a refractory inflammatory disease; its cause is unknown and it presents with repeated acute inflammation in various organs throughout the body. Its 4 major manifestations are oral aphthae, ocular manifestations, skin manifestations, and genital ulcers. Frequently appearing in the mongoloid population in the vicinity of the Silk Road, the disease is rare in Europeans and Americans (Fig. 1). In Japan, registered patients are described as numbering about 18,000 people,[2,3] however, this number is assumed to be even higher if potential patients are also included. The causes of Behçet's disease are still unknown, but the mechanism of its pathogenesis is becoming clearer.

Demographic Characteristics/ Epidemiology in Japan

Epidemiology

The male-to-female patient ratio in Japan is 0.98.
Total patients in Japan: 18,300 people (1991), 19,800 people (1996).
135 people out of a population of 1 million.

Distribution

Prevalent along the Silk Road, 30–45 degrees north on the Eurasian landmass.
Prevalent in the north of Japan.
Widely prevalent in Turkey, Jordan, Syria, Israel, Lebanon, and Saudi Arabia. Also found in the Mediterranean, Spain, Portugal, Greece, and Italy. Not found in Caucasians of Northern European decent and Sub-Sahara Africans.
Not found in Southeast Asia or in Hawaiians or Brazilians of Japanese descent.
Not found in any of the races in North, Central, or South America.

*1 Department of Ophthalmology, Yokohama City University School of Medicine, Yokohama
Correspondence to: Takahiko Hayashi MD, Department of Ophthalmology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan. Tel: 81-45-787-2683, Fax: 81-45-781-9755, E-mail: amg-igf@goo.jp

Table 1 Diagnostic criteria for Behçet's disease according to the Behçet's Disease Research Committee of Japan

Behçet's disease clinical diagnostic criteria (2003 revision)

(1) Major manifestations

① Recurrent aphthae of oral mucosa
② Skin manifestations
  (a) Erythema nodosum
  (b) Subcutaneous thrombophlebitis
  (c) Folliculitis-like rash, acne-like rash
    Referential finding: enhanced skin irritability
③ Ocular manifestations
  (a) Iridocyclitis
  (b) Uveoretinitis (retinochoroiditis)
  (c) If the following findings are present, they conform to (a) (b)
    Posterior synechia, lens pigmentation, chorioretinal atrophy, optic atrophy, complicated cataract, secondary glaucoma, or phthisis bulbi considered to be the progress of (a) (b)
④ Genital ulcers

(2) Minor manifestations

① Arthritis without deformation or stiffness
② Epididymitis
③ Digestive tract sores as typified by ileocecal ulcers
④ Vascular lesions
⑤ Moderate or more severe CNS lesions

(3) Criteria for diagnosis of the type of disease

① Complete type
  4 major manifestations appear in the course of the illness
② Incomplete type
  (a) 3 major manifestations or 2 major and 2 minor manifestations appear in the course of the illness
  (b) Typical ocular manifestations and 1 major or 2 minor manifestations appear in the course of the illness
③ Possible type
  Some major manifestations appear but do not qualify as the incomplete type and typical minor manifestations repeat or worsen
④ Specific lesions
  (a) entero-Behçet's disease—The presence/absence of abdominal pain and occult blood test result will be listed.
  (b) vasculo-Behçet's disease—Impairment of large arteries, small arteries, or large & small arteries will be listed.
  (c) neuro-Behçet's disease—The presence/absence of headaches, palsy, cerebrospinal-type symptoms, psychiatric manifestations, etc. will be listed.

(4) Test once for HLA-B51 (B5) positivity

  The type of HLA should be listed

(5) Laboratory findings for reference (not mandatory)

① Negative/positive in a positive skin pathergy test
  A relatively large injection needle of 22–18 G will be used
② Negative/positive on a prick test with a streptococcus vaccine
  Hypersensitivity to streptococcus
  Many patients with Behçet's disease display strong hypersensitivity to oral streptococci like Streptococcus sanguinis, so in a prick test (fine 26 G needle) with Streptococcus sanguis antigen, this can be seen as a strong flare reaction 20–24 hrs later.
③ Inflammatory response
  Enhanced level of sedimentation, positive serum CRP, increased WBC count in peripheral blood, rise in complement titer
④ HLA-B51(5) positive
⑤ Pathological findings
  With acute-stage erythema nodosum, cells infiltrating because of septal panniculitis are due to the infiltration of polymorphonuclear and mononuclear leukocytes.
  Initially, polymorphonuclear leukocytes are prevalent but infiltration is mainly of mononuclear leukocytes, presenting an image of "lymphocytic vasculitis."
  This may also be accompanied by necrotizing vasculitis, which suggests the possibility of systemic vasculitis, so the presence/absence of this vasculitis will be examined.

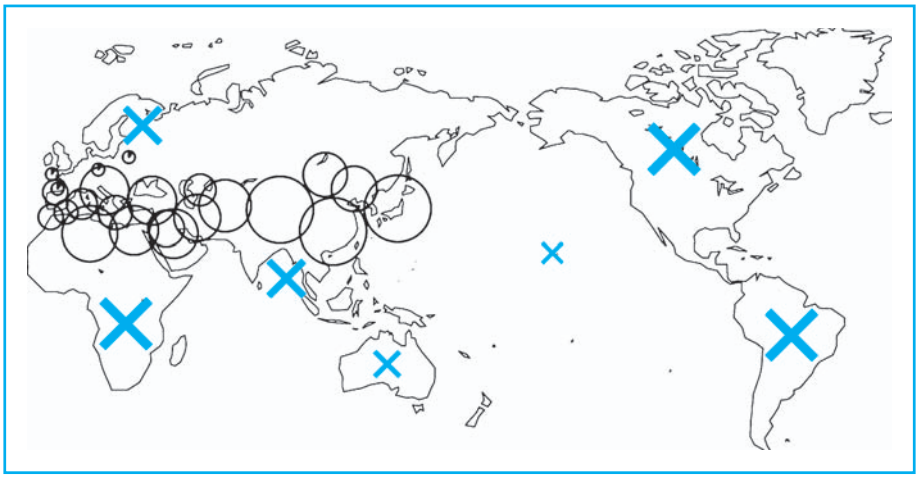

Fig. 1 Global distribution of Behçet's disease

Plotting the global distribution of Behçet's disease on the chart indicates that countries with a prevalence of this disease are concentrated in the region along the Silk Road from 30 to 45 degrees north. With its eastern end in Japan, the region covers East Asia, Central Asia, Eurasia, West Asia, and then the Mediterranean before reaching its western end in Morocco, Spain, and Portugal. The ○'s indicate countries with a prevalence of Behçet's disease and the ×'s indicate regions where it is only rarely seen. (Studies on exogenous and endogenous factors associated with various ocular diseases[6])

Table 2 Major manifestations

A)	Recurrent aphthae of the oral mucosa:	98.2%
B)	Skin manifestations: Erythema nodosum Subcutaneous thrombophlebitis Folliculitis-like rash	87.1%
C)	Ocular manifestations: Iridocyclitis Uveoretinitis, etc.	69.1%
D)	Genital ulcers:	73.2%

(Results of a National Epidemiological Survey of Patients with Behçet's Disease (First report)[2])

Table 3 Minor manifestations

A)	Arthritis without deformation or stiffness:	56.9%
B)	Epididymitis:	6.0%
C)	Digestive tract sores as typified by ileocecal ulcers:	15.5%
D)	Vascular lesions:	8.9%
E)	Moderate or more severe CNS lesions:	11.0%

(Results of a National Epidemiological Survey of Patients with Behçet's Disease (First report)[2])

Epidemiology by type of disease (1991)[2]

The complete type accounts for 28.9%, the incomplete type for 55.3%, and possible cases account for 8.4%.

Epidemiology by manifestation (1991)[2]

According to a large-scale epidemiological study[2] that compared cases in 1972 and 1991, many patients having the incomplete type with ocular manifestations were men (sex ratio: 1.87); many patients having the incomplete type with genital ulcers were women (sex ratio: 0.42).

Incidence of major and minor manifestations (1991)[2]

Recurrent aphthae of the oral mucosa manifested in 98.2%, skin manifestations in 87.1% (erythema nodosum, subcutaneous thrombophlebitis, folliculitis-like rash, and ocular manifestations in 69.1%, and genital ulcers in 73.2%). (see Table 2)

Arthritis without deformation or stiffness manifested in 56.9%, epididymitis in 6.0%, digestive tract sores as typified by ileocecal ulcers in 15.5%, vascular lesions in 8.9%, and moderate or more severe CNS lesions in 11.0%. (see Table 3)

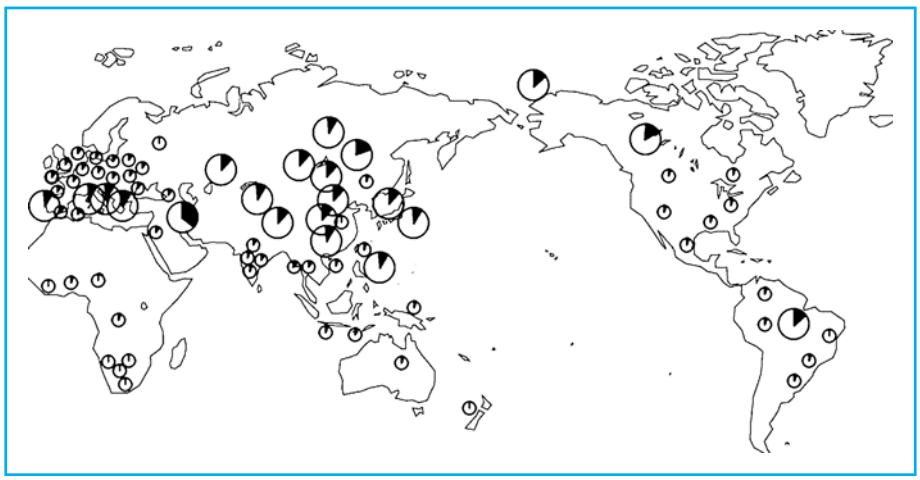

Fig. 2 Global distribution of HLA-B51

HLA-B51 is frequently seen in East Asia, e.g. Japan, Central Asia, Eurasia, West Asia, and the Mediterranean. However, it is infrequent in Sub-Sahara Africa and in Europe and the US where Caucasians live. In addition, HLA-B51 is rare in Southeast Asia. Thus, the global distribution of the genetic factors of HLA-B51 coincides impressively with the global distribution of Behçet's disease. (Studies on exogenous and endogenous factors associated with various ocular diseases[6])

Pathology of Behçet's Disease

The pathogenesis of Behçet's disease clearly involves neutrophil dysfunction,[4] lymphocyte abnormalities, cytokine abnormalities,[5] immunological abnormalities, etc. Genetically, the disease is, based on an examination of HLA-B51 and related genes, a multifactorial illness in which the disease arises with some external environmental factors at work based on specific intrinsic genetic factors.[6] The distribution of HLA-B51 is shown in Fig. 2. Traversing race, Behçet's disease is markedly correlated with the HLA-B51 antigen—a specific type of HLA, the human form of the major histocompatibility antigen—and is highly positive for HLA-B51; HLA-B51 is considered to play a major role in the pathogenesis of the disease. In addition, we have proffered the hypothesis that asparagine at position 63 and phenylalanine at position 67, amino acids specific to the HLA-B51 molecule, play a major role in the onset of this disease. In actuality, HLA-B51 carriers have a relative risk of suffering Behçet's disease of 17.1,[7] which is extremely high. Additionally, the MICA (MHC class I chain-related gene A) gene is located in very close proximity to the HLA-B gene (slightly centromeric at 46 kb) and is in strong linkage disequilibrium with the HLA-B gene. The MICA gene is an HLA-like molecule and has 30% amino acid homology with the HLA class I antigen. The MICA molecule is primarily expressed in intestinal epithelium, vascular endothelial cells, keratinocytes, etc. and coincides with local inflammation in Behçet's disease. We previously analyzed the MICA gene and clarified the fact that the MICA-A6 allele (MIC-A*009 allele) increases significantly in patients with Behçet's disease, suggesting its secondary involvement in the onset of the disease.[8–10] Recent studies have also indicated that the A6 allele of the MICA molecule (and particularly MICA-A*009) displays a high level of affinity for HLA-B51,[8–12] and further analysis is required with regard to the involvement of the MICA molecule in the onset of this disease. Additionally, immunological abnormalities due to self- and/or bacterial/microbial heat shock proteins (HSPs) are also critical. T lymphocytes of patients with Behçet's disease who have ocular manifestations are specific and highly reactive to self HSP and exogenous HSP with cross-reactivity to self HSP and actively produce proinflammatory cytokines and neutrophil-directed cytokines.[13] Based on reports that TNFα production is significantly

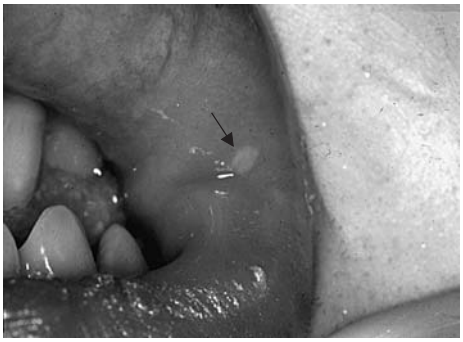

Fig. 3 Typical oral aphtha is apparent (→)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)

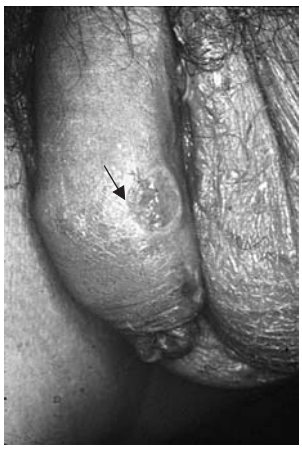

Fig. 4 Typical genital ulcer (→)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)

enhanced in the active stage of ocular manifestations[14–16] and that the serum concentration of TNFα is higher regardless of whether oral aphthae and erythema nodosum are present, TNFα is also involved in the pathology of Behçet's disease. Though in the clinical trial stage, the efficacy of anti-TNFα chimeric antibody (infliximab), a form of anti-TNFα antibody therapy, as a therapeutic agent has also been confirmed.[17,18]

Diagnostic Criteria for Behçet's Disease

Nevertheless, there are currently no laboratory findings useful in and specific to the diagnosis of Behçet's disease at this time. HLA-B51 antigen is positive in about 60% of patients, which is somewhat high, and this positivity can serve as a reference, but it is positive in about 15% of healthy individuals, so this result cannot be considered definitive.[7] Thus, Behçet's disease is diagnosed based on a combination of clinical manifestations. Diagnostic criteria in Japan and the West differ. International diagnostic criteria[20] by an International Study Group cite recurrent oral aphthae as a mandatory manifestation; with this, if 2 of 4 items—genital ulcers, ocular manifestations, skin manifestations, or a positive pathergy test—are satisfied, then the condition can be diagnosed as Behçet's disease. Ocular manifestations have a high specificity in Behçet's disease; the complete type in Japan's diagnostic criteria agrees 100% with international diagnostic criteria but incomplete Behçet's with ocular manifestations is excluded. In addition, the positive pathergy test, one of the international diagnostic criteria, is 43.8%, which is not frequent enough to be considered a major manifestation in Japan,[2] so cases that cannot be definitively diagnosed as Behçet's disease with Japan's diagnostic criteria can be diagnosed as Behçet's disease with international diagnostic criteria.

Thus, future reappraisal of international diagnostic criteria is probably required.

In Japan, criteria are divided into major and minor manifestations and the disease is classified as a complete, incomplete, possible, or specific type based on the combination of those manifestations (Table 1).

Clinical Features

This section cites a 1991 Ministry of Health and Welfare Committee report and notes the incidence of major and minor manifestations of Behçet's disease (Tables 2 and 3).

Recurrent aphthae (included in major manifestations)

Oral aphthae (Fig. 3) are the first manifestation to appear in Behçet's disease. Aphthae may be present singly or clustered in the buccal mucosa in the mouth, on the gingiva, on the tongue, inside the lips, on the palate, etc. They may also appear on the tonsils, pharynx, and esophagus. The aphtha is a small, round ulcer with a clearly defined border and is painful. Characteristic of aphthae is that they heal in 1–2 weeks without

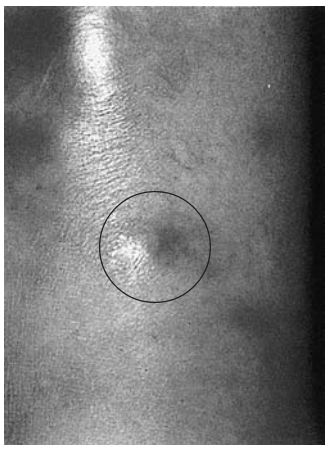

Fig. 5 Erythema nodosum (portion circled with a ○)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)

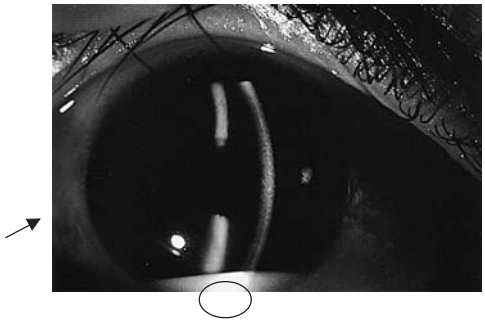

Fig. 6 Recurrent hypopyon iridocyclitis
Ciliary hyperemia (→) and a hypopyon (circled portion) are apparent.

scarring but repeatedly reappear. During recurrence, the location of the aphtha often differs. However, aphthae are not specific to Behçet's disease and are no different from chronic recurrent aphthae in ordinary individuals, so caution is required since, in the initial stages, they are simply regarded as stomatitis and are left untreated. Oral aphthae are the most frequent initial manifestation of Behçet's disease.[2] They often appear 10–15 years prior to definitive diagnosis and have a final incidence of almost 100%.[2]

Genital ulcers (included in major manifestations)

Genital ulcers (Fig. 4) are a characteristic finding of Behçet's disease. The ulcers are painful with a clear boundary and also cause considerable pain. They occur on the penis, scrotum, labia minora, vaginal walls, in the anal region, etc. They heal in 1–2 weeks, but unlike oral aphthae and erythema nodosum, scarring may remain even after the site has healed. The occurrence of ulcers at such sites is rare for other illnesses, so this is a specific finding that strongly suggests Behçet's disease.

Skin manifestations (major manifestations)

With regard to skin manifestations, major manifestations are erythema nodosum (Fig. 5), subcutaneous thrombophlebitis, and folliculitis-like rash, and a positive pathergy test is a referential finding.

Erythema nodosum is painful erythema of 1-several cm that favors the extensor aspects of the lower extremities and is characterized by a somewhat raised area. It heals in about 1–2 weeks without scarring but repeatedly recurs.

A folliculitis-like rash involves circular follicular sterile pustules of several mm and often appears on the face, trunk, and at sites subjected to mechanical irritation. However, such skin manifestations are not findings specific to Behçet's disease and are not readily differentiated from those due to other illnesses.

When pricked with a needle, the area forms a sterile pustule after 24–48 hours; this is called a positive pathergy test. Occurrence in Japan is low at 43.8%,[2,24] but a foreign source (Israel) did find the test to have a high sensitivity and specificity.[21]

Skin irritability is observed along with purulence and development of a rash.

Ocular manifestations

The age at onset of ocular manifestations is often in the 30s, and these manifestations tend to be severe in men.

One year after onset, 40% of patients have visual acuity of less than 0.1; after 8 years, 80% of patients have visual acuity of less than 0.1. After 10 years, 40% of cases become blind.[2,22,23]

Iridocyclitis type:
recurrent hypopyon iridocyclitis

Acute non-granulomatous inflammation occurs in the anterior eye (iris, ciliary bodies, etc.) and often forms a hypopyon (Fig. 6). The hypopyon may be seen by the patient himself while looking in a mirror when an attack occurs or it may be

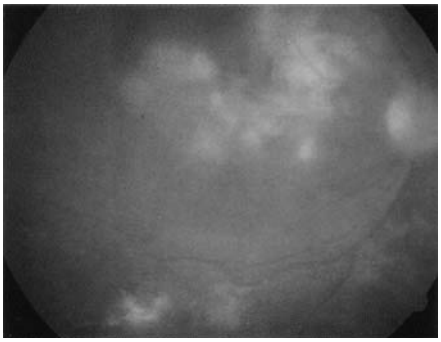

Fig. 7 Fundal attack
Bleeding and exudate are apparent.

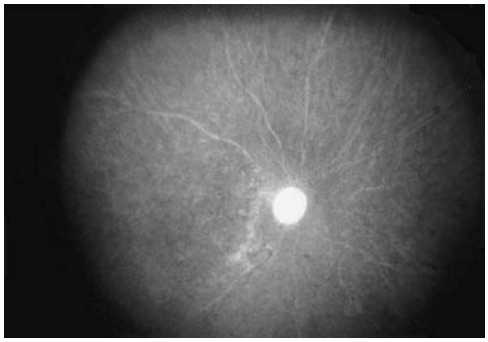

Fig. 8 End-stage fundus photography
Vessels appear as white lines due to vascular occlusion; optic and chorioretinal atrophy are apparent.

noted by family. A hypopyon also occurs with HLA-B27-associated uveitis and uveitis in diabetes, ulcerative colitis, Crohn's disease, and herpes virus infection but it is naturally frequent in Behçet's disease. A hypopyon resulting from Behçet's disease is facile and moves in accordance with gravity, but when the patient lays on his side, it moves horizontally and a niveau is formed at an angle. In contrast, a hypopyon resulting from HLA-B27-associated uveitis has a large amount of fibrin, is sticky, and does not move, so this serves as a reference for differentiation of the two. At times, an angle hypopyon can be seen with a goniolens. Posterior synechia is found in 32%[22–24] and is more frequent than with other types of uveitis. With complete posterior synechia, moreover, iris bombe occurs in 71%. When ciliary body function declines, rubeosis iridis and phthisis bulbi may occur. Keratic precipitates are infrequent, but even if they are detected, they do not become mutton-fat keratic precipitates. Peripheral anterior synechia is also seen, but it does not lead to "tenting."

In Behçet's disease, the iridocyclitis type accounts for about 20% of ocular manifestations overall. Patients often complain of blurred vision but may have partial whitening of the visual field and be unable to see. Initially, symptoms often clear up within several weeks but may become prolonged with repeated attacks.

Uveoretinitis type:
vasculitis with bleeding and exudate

Repeated inflammation occurs in the choroid and retina, and permanently blurred vision remains. About 5 years later the peak of inflammation occurs, after which the inflammation winds down. Retinal vasculitis with bleeding and exudate is found in fundoscopy of the uveoretinitis type (Fig. 7). Such fundal attacks can occur anywhere in the retina. Exudate runs along retinal vessels and displays the same distribution as bleeding. In addition to Behçet's disease, such findings are also seen in viral retinochoroiditis, tuberculous retinochoroiditis, etc. There are instances where visual acuity of 1.0 may drop to less than 0.1 with just one attack. However, even if visual acuity drops to the hand motion level, visual acuity returns in a considerable number of cases once an antiinflammatory is given for several weeks to several months. There are frequently instances in which 80 to 90% of the previous visual acuity returns. However, visual acuity often gradually declines with repeated attacks and often ultimately results in blindness.[2,22,23] The Ministry of Health, Labour and Welfare's Behçet's Disease Research Committee previously stated that individuals in which ocular manifestations appeared would have visual acuity of less than 0.1 in about 8 years; this condition would result in blindness for close to 40% of individuals in about 10 years. However, visual prognosis is gradually improving with the recent moderation of Behçet's disease and development of new therapies. When the condition is complicated with uveoretinitis, posterior sub-Tenon's injection of a steroid is added. And when frequent attacks are seen, systemic agents are also incorporated. Colchicine and cyclosporine are systemic agents, but orally administered medication is selected depending on the patient's age, level of disease activity, the wishes of the patient,

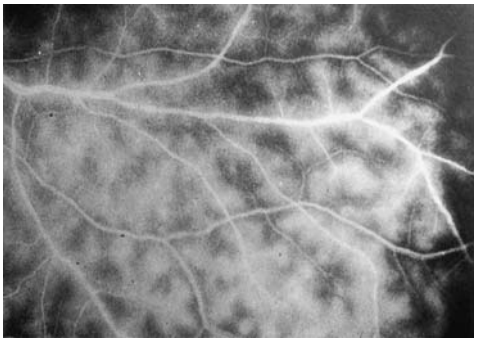

Fig. 9 Fluorescein angiography
Vascular leakage in a fern pattern is apparent

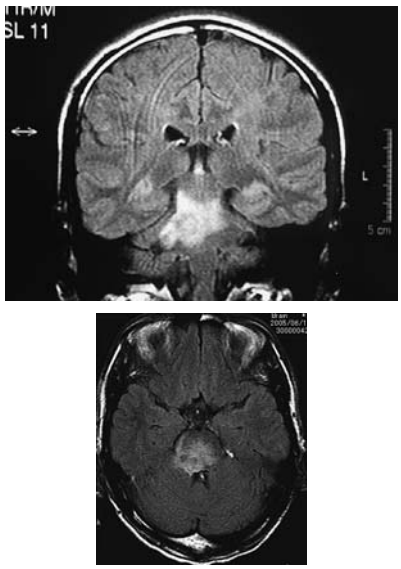

Fig. 10 Neuro-Behçet's
Hyperintensity presents in T2 MRIs

and the type of disease. If there is a possibility of pregnancy, colchicine, which is teratogenic, is contraindicated. The introduction of cyclosporine is examined when the condition is highly active, but the agent must be carefully administered with an initial dose of 2–3 mg/kg/day and the trough level should be observed periodically. With neuro-Behçet's, however, cyclosporine is contraindicated. In addition, concomitant use of colchicine and cyclosporine is contraindicated because it may induce myopathy.

Ocular prognosis and end-stage fundus findings

End-stage fundus findings for Behçet's disease are chorioretinal and optic atrophy (Fig. 8).

The portions of the retina and choroid are where fundal attacks have occurred because of Behçet's disease atrophy. In addition, bloodflow is impaired by the inflammation of vessels and occlusive vasculitis occurs; as this progresses, bloodflow is disrupted; retinal vessels whiten and appear as white lines. Cells of the retina and choroid in whitened vascular areas are damaged and regions suffering chorioretinal atrophy cause a decrease in visual performance, so portions of the visual field that cannot be seen gradually increase with attacks and the visual field also narrows. However, ocular attacks occur randomly in the fundus, so this is fundamentally different from the narrowing of the visual field that occurs in glaucoma as optic nerves are damaged. Thus, narrowing of the visual field gradually progresses with ocular attacks.

Fluorescein angiography

Fluorescein angiography is performed to diagnose Behçet's disease and determine the progress of the disease. Pathology involves retinal vasculitis (and particularly thrombophlebitis); an indicative finding is fluorescein leakage in a fern pattern, i.e. exuding of the fluorescent agent (Fig. 9). In addition, occlusive vasculitis, avascular areas with that vasculitis, neovascularization, etc. are seen.

Other generalized manifestations

There are 5 types of minor manifestations. Arthritis appears in close to 60% of cases, meaning that its frequency is close to that of a major manifestation. It is characterized by a lack of deformation or stiffness in major joints and a lack of morning stiffness, which differentiates it from rheumatoid arthritis. Other manifestations include epididymitis, ulcers of the ileocecum (entero-Behçet's), vascular lesions, and neurological manifestations. These all have a frequency of about 10% (Table 3). Since they can be life-threatening, entero-, vasculo-, and neuro-Behçet's disease require vigilance and are classified into specific types of the disease. Neurological manifestations appear last in Behçet's disease and often in men; they occur after about 5–10 years have passed since the onset of this disease. With characteristic CNS manifestations, lesions of the base of the brain, i.e. the brainstem, midbrain, and pons, occur in 80–90%. Brainstem and cerebellar manifestations such as motor paralysis of the hands and feet, hemiplegia and headaches, staggering, gait disturbance, dysar-

thria and diplopia and psychiatric manifestations such as personality changes are seen. Thus, if patients complain of headaches, staggering, or dysarthria, detailed examinations should be quickly performed. An MRI is useful for testing (Fig. 10). In terms of vascular manifestations, inflammatory or thrombotic occlusions occur in large and medium-sized vessels and sometimes form an aortic aneurysm; this is a deadly complication. Use of cyclosporine therapy has recently become widespread, often leading to problems with the induction or promotion of neurological manifestations of Behçet's disease and differentiation from CNS manifestations that are adverse effects of cyclosporine itself.

References

1. Saylan T. Life story of Dr. Hulusi Behçet. Yonsei Med J. 1997; 38(6):327–332.
2. Nakae K, et al. Results of a National Epidemiological Survey of Patients with Behçet's Disease (First report): Estimation of Prevalence and Morbidity. Behçet's Disease Research Committee, Japanese Ministry of Health and Welfare, Collected Papers-1992. 1993:40–46.
3. Suzuki Kurokawa M, Suzuki N. Behçet's disease. Clin Exp Med. 2004;4(1):10–20.
4. Direskeneli H. Behçet's disease: infectious aetiology, new autoantigens, and HLA-B51. Ann Rheum Dis. 2001;60(11): 996–1002.
5. Mege JL, Dilsen N, Sanguedolce V, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol. 1993;20(9):1544–1549.
6. Ohno S, Studies on exogenous and endogenous factors associated with various ocular diseases. Nippon Ganka Gakkai Zasshi 2005;109(12):885–916.
7. Chajek-Shaul T, Pisanty S, Knobler H, et al. HLA-B51 may serve as an immunogenetic marker for a subgroup of patients with Behçet's syndrome. Am J Med. 1987;83(4):666–672.
8. Mizuki N, Yabuki K, Ota M, et al. Analysis of microsatellite polymorphism around the HLA-B locus in Iranian patients with Behçet's disease. Tissue Antigens. 2002;60(5):396–399.
9. Yabuki K, Mizuki N, Ota M, et al. Association of MICA gene and HLA-B*5101 with Behçet's disease in Greece. Invest Ophthalmol Vis Sci. 1999;40(9):1921–1926.
10. Mizuki N, Inoko H, Ohno S. Molecular genetics (HLA) of Behçet's disease. Yonsei Med J. 1997;38(6):333–349.
11. Park SH, Park KS, Seo YI, et al. Association of MICA polymorphism with HLA-B51 and disease severity in Korean patients with Behçet's disease. J Korean Med Sci. 2002;17(3):366–370.
12. Picco P, Porfirio B, Gattorno M, et al. MICA gene polymorphisms in an Italian paediatric series of juvenile Behçet's disease. Int J Mol Med. 2002;10(5):575–578.
13. Direskeneli H, Saruhan-Direskeneli G. The role of heat shock proteins in Behçet's disease. Clin Exp Rheumatol. 2003;21: S44–S48.
14. Gul A. Behçet's disease: an update on the pathogenesis. Clin Exp Rheumatol. 2001;19:S6–S12.
15. Yamashita N, Kaneoka H, Kaneko S, et al. Role of gammadelta T lymphocytes in the development of Behçet's disease. Clin Exp Immunol. 1997;107:241–247.
16. Mege JL, Dilsen N, Sanguedolce V, et al. Overproduction of monocyte-derive TNF-a, IL-6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol. 1993;20:1544–1549.
17. Lanthier N, Parc C, Scavennec R, et al. Infliximab in the treatment of posterior uveitis in Behçet's disease. Long term follow up in four patients. Presse Med. 2005;34(13):916–918.
18. Nakamura S, Ohno S. Anti-tumor necrosis factor alpha antibody in the treatment of Behçet's disease. Int Ophthalmol Clin. 2005; 45(2):179–189.
19. Hamzaoui K, Hamzaoui A, Guemira F, et al. Cytokine profile in Behçet's disease patients. Relationship with disease activity. Scand J Rheumatol. 2002;31(4):205–210.
20. International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335:1078–1080.
21. Friedman-Birnbaum R, Bergman R, et al. Sensitivity and specificity of pathergy test results in Israeli patients with Behçet's disease. Cutis. 1990;45(4):261–264.
22. Ando K, Fujino Y, Hijikata K, et al. Clinical aspects of Behçet's disease—epidemiological features and visual prognosis. Nippon Ganka Gakkai Zasshi. 1997;101(10):814–818.
23. Mishima S, Masuda K, Izawa Y, et al. The eighth Frederick H. Verhoeff Lecture. presented by Saiichi Mishima, MD. Behçet's disease in Japan: ophthalmologic aspects. Trans Am Ophthalmol Soc. 1979;77:225–279.
24. Nakae K, Hashimoto T, Inaba G, et al. Results of a National Epidemiological Survey of Patients with Behçet's Disease (Second report): Relationship between clinical epidemiological results and HLA-B51. Behçet's Disease Research Committee, Japanese Ministry of Health and Welfare, Collected Papers-1992.1993:70–82.

Case Report

A Case of Pneumothorax in Which Progression of Reexpansion Pulmonary Edema Was Arrested

JMAJ 49(7・8): 269–271, 2006

Makoto Nonaka,[*1] Koji Maezawa,[*1] Yasushi Koike,[*1] Toshiyuki Hatakeyama,[*1] Hitoshi Soda,[*1] Osamu Sakurai,[*1] Yasuo Ishida,[*1] Kiyoshi Hataya[*1]

Abstract

We report a case of pneumothorax secondary to emphysema in which we arrested reexpansion pulmonary edema. The patient was a 58-year-old male. A chest drainage tube was inserted to manage the secondary left pneumothorax, but further aggravation of dyspnea and frothy airway secretions were observed shortly after drainage. Because reexpansion pulmonary edema was suspected, we intentionally chose to perform oxygen administration and opening of the drain. As symptoms subsided, the patient was put in a right lateral decubitus, and gradual expansion of the lungs was attempted. As chest X-ray showed suspected edema in the left lung, a potent diuretic was administered. Since no exacerbation of symptoms or decrease in transcutaneous arterial oxygen pressure was noted, the patient was kept under observation without requiring further medication. In a clinical situation where a patient shows aggravation of dyspnea and appearance of frothy sputum during reexpansion of collapsed lungs, it is critical to prevent the development of fatal reexpansion pulmonary edema by arresting rapid expansion of the lungs and avoiding the increase in blood flow into the reexpanding lungs.

Key words Pulmonary edema, Pneumothorax, Pulmonary blood flow, Blood vessel permeability, Dyspnea, Frothy sputum

Introduction

Reexpansion pulmonary edema (RPE) is a type of pulmonary edema that may develop when collapsed lungs are reexpanded. It is a rare but fatal condition. RPE is less likely to occur during reexpansion after a short period of pulmonary collapse, and the incidence increases after prolonged pulmonary collapse.[1] In this article, we report a case in which we arrested the development of RPE following chest drainage in a patient with pneumothorax secondary to pulmonary emphysema.

The Case

The patient was a 58-year-old man, who had been treated by a local physician for pulmonary emphysema. Precordial pain and dyspnea developed about 9 a.m., and the patient visited our hospital at about 16:00 of the same day because of aggravating dyspnea. Chest X-ray revealed a left pneumothorax (Fig. 1), which was considered to have been present for about 7 hours. A chest drainage tube was inserted to manage the secondary pneumothorax, but further aggravation of dyspnea and the sudden appearance of frothy airway secretions were observed shortly after drainage. Because RPE was suspected, we intentionally chose to open the chest tube to release the negative pressure in the left thoracic cavity for the purpose of preventing mechanical damage to pulmonary alveoli and avoiding the increase in pulmonary blood flow that might result from the rapid reexpansion of the lungs.

*1 Department of Surgery, Yokohama Asahi Central & General Hospital, Yokohama
Correspondence to: Makoto Nonaka MD, Department of Surgery, Yokohama Asahi Central & General Hospital, 4-20-1 Wakabadai, Asahi-ku, Yokohama, Kanagawa 241-0801, Japan. Tel: 81-45-921-6111, Fax: 81-45-921-4931, E-mail: nonakama@asahi-hp.jp

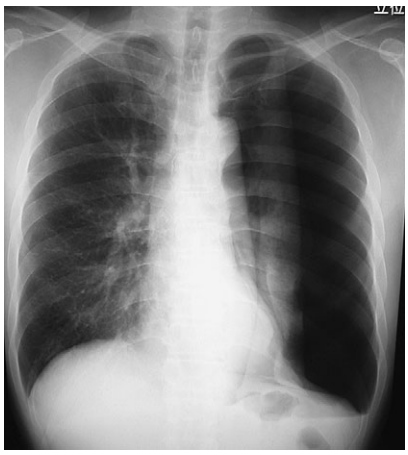

Fig. 1 Chest X-ray showing a left pneumothorax
Pleural adhesion is seen in the apical segment, and complete lung collapse has not taken place.

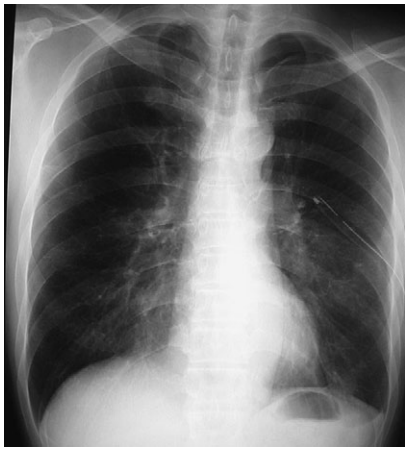

Fig. 2 Chest X-ray after chest drainage for the left pneumothorax
While the left lung is expanded well, pulmonary edema in the left lung is suspected.

Oxygen was administered and the patient was put in a sitting position. As the symptoms subsided in about 10 minutes, the patient was put in a right lateral decubitus, and gradual expansion of the lungs was attempted by water-seal drainage and repeated drain clamping. During drain clamping, the development of subcutaneous emphysema was prevented by strong compression on the drain insertion site. As chest X-ray showed suspected edema in the left lung (Fig. 2), a potent diuretic was administered. Since no exacerbation of symptoms or decrease in transcutaneous arterial oxygen pressure was noted, the patient was kept under observation without requiring further medication. CT examination on the following day did not indicate apparent aggravation of signs suggesting pulmonary edema (Fig. 3). Although the complete disappearance of ground-glass opacities in the lungs was achieved subsequently, the pulmonary air leak did not disappear. Consequently, thoracoscopic partial lung resection under general anesthesia was performed 11 days after drainage. Postoperative examinations demonstrated the disappearance of pulmonary air leak and the absence of RPE. The chest tube was removed 2 days after operation. As of the time of this writing, 7 months after surgery, the patient has been doing well without any relapse of the pneumothorax or the development of pulmonary edema.

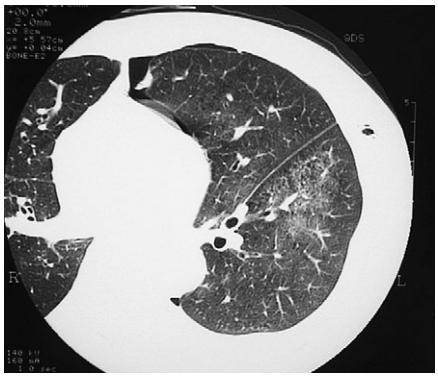

Fig. 3 Chest CT after chest drainage for the left pneumothorax
While the left lung is expanded well, pulmonary edema in the left lung is suspected.

Discussion

Treatment methods for pneumothorax include rest, thoracocentesis, chest drainage, and surgery. The guidelines and consensuses in such countries as the U.S. and the U.K. state that chest drainage is the method of choice for secondary pneumothorax resulting from pulmonary emphysema or pulmonary fibrosis.[2,3] In the present case, we selected hospitalization and chest drainage following these examples.

RPE generally tends to develop when the

lungs are reexpanded rapidly after a long period of pulmonary collapse.[4] This fact suggests the involvement of the mechanical and chemical damage to pulmonary microcirculation during prolonged pulmonary collapse, resulting in enhanced blood vessel permeability. In the present case, RPE developed as shortly as about 7 hours after the onset of symptoms. Although the cause of this early development of RPE is unknown, a reasonable explanation is that damage to pulmonary alveoli and microcirculation might have existed as a result of pulmonary emphysema. Rapid reexpansion of collapsed lungs is considered likely to induce RPE, as it promotes the influx of pulmonary arterial blood.[5,6] In our case, early symptoms of RPE such as aggravation of dyspnea and appearance of frothy sputum were observed despite the fact that the lungs were reexpanded gradually using the water-seal method after chest tube insertion. This observation coincides with various authors reporting that RPE can develop even during gradual reexpansion of the lungs, as the development of RPE is dictated by blood vessel permeability and pulmonary blood flow.[7] For this reason, we should keep the patient under close observation for a certain period after chest tube insertion, remembering that RPE can develop in any situation. RPE is most likely to occur during the 24 hours, particularly during the first hour, after reexpansion of the lungs, and care should be taken not to leave the patient unattended during this period.[8]

Once RPE has become established, the condition should be treated with diuretics, cardiotonics, and bronchodilators, as well as artificial respiration management. The aggravation of RPE may be prevented by the timely detection of early symptoms and stopping pulmonary blood flow into the reexpanding lungs. After these measures are taken, medication to reverse the enhanced permeability of blood vessels in the lungs should be selected appropriately.[9] In the present case, we attempted to address the aggravation of dyspnea shortly after chest drainage by opening the chest drain to release the negative pressure in the left thoracic cavity, induce the collapse of the left lung and blood vessels therein as much as possible, and limit the blood flow into the left lung. In this procedure, the open end of the drain tube was protected with gauze to reduce the risk of retrograde infection. Subsequently, the patient was put in a sitting position and oxygen was administered to improve dyspnea and lessen anxiety of the patient, and then he was put in a right lateral decubitus as promptly as possible. The purpose of this maneuver was to use gravitation for increasing blood flow in the right lung and decreasing that in the left lung. When complete collapse of the left lung is hindered by intrathoracic adhesion as in this case, it is impossible to stop the blood flow to the lower left lung field as long as the patient is in a sitting position.

Our judgment that the patient was about to develop RPE was based on clinical and imaging findings. We cannot say for sure whether or not the patient would have developed RPE without the treatment described above. However, fully developed RPE is often fatal, and treatment of the patients after successful life saving would require much time.[10] We report this case to emphasize the fact that physicians performing thoracic drainage should always consider the possibility of RPE, and any aggravating signs or symptoms observed after drainage should be treated promptly.

References

1. Genofre EH, Vargas FS, Teixeira LR, et al. Reexpansion pulmonary edema. J Pneumol. 2003;29:101–106.
2. Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119:590–602.
3. Henry M, Arnold T, Harvey J. BTS guidelines for the management of spontaneous pneumothorax. Thorax. 2003;58 (Suppl II): ii39–ii52.
4. Jackson RM, Veal CF. Review: re-expansion, re-oxygenation, and rethinking. Am J Med Sci. 1989;298:44–50.
5. Sivrikoz MC, Tuncozgur B, Cekmen M, et al. The role of tissue reperfusion in the reexpansion injury of the lungs. Eur J Cardio-Thorac Surg. 2002;22:721–727.
6. Sprung CL, Loewenberg JW, Baier H, et al. Evidence for increased permeability in reexpansion pulmonary edema. Am J Med. 1981;71:497–500.
7. Aghajanzadeh M, Dadkhah-Tirani H, Shafaroodi A. Reexpansion pulmonary edema and its treatment approaches. Arch Iranian Med. 2003;6:208–211.
8. Jantz MA, Sahn SA. Pleural disease in the Intensive Care Unit. J Intensive Care Med. 2000;15:63–89.
9. Spragg RG. Acute lung injury in 2003. Acta Pharmacol Sin. 2003;24:1288–1291.
10. Nonaka M, Hataya K. Saibouchousei haisuishu [Reexpansion Pulmonary Edema]. The Journal of the Japan Medical Association. 2006;134:1955–1958. (in Japanese)

A Case of Subclinical Central Diabetes Insipidus Unmasked by Pregnancy

JMAJ 49(7・8): 272–275, 2006

Ryuji Katase,[*1] Yuji Moriwaki,[*1] Sumio Takahashi,[*1] Zenta Tsutsumi,[*1] Taku Inokuchi,[*1] Tuneyoshi Ka,[*1] Tetsuya Yamamoto[*1]

Abstract

A 30-year-old woman was referred to our division because of polyuria and polydipsia, and was treated for transient diabetes insipidus associated with her pregnancy. At the time of consultation, the patient was at 34 weeks of gestation and being followed by an obstetrician. Her urine output during hospitalization ranged from 5–8 L/day. On examination, she was apparently in good health without definite evidence of dehydration, and her blood pressure was 110/80 mmHg and pulse rate was 114/minute. Laboratory results disclosed the following values: Total protein 6.9 g/dL, serum sodium 155 mmol/L, potassium 4.1 mmol/L, chloride 123 mmol/L, and serum and urine osmolality 316 mOsm/L and 138 mOsm/L, respectively, suggesting hemoconcentration. MR-CT imaging of the pituitary gland showed disappearance of a high intensity signal from the posterior lobe in a T_1-weighted sequence, suggesting ADH depletion. A tentative diagnosis of central diabetes insipidus was made and the patient was given 1-desmino-8D-arginine-vasopressin (dDAVP), after which her urine output decreased significantly and serum and urine osmolality returned to normal ranges. She gave birth to a 3002 g male infant 5 weeks later. The labor was uneventful, however, water-deprivation and hypertonic saline challenge tests performed 2 and 3 weeks later, respectively, showed incomplete central diabetes insipidus. Following the birth, urine output decreased spontaneously and dDAVP was no longer needed, although MR-CT imaging of the pituitary gland showed that disappearance of the high intensity signal in the posterior lobe in a T_1-weighted sequence persisted.

An association between pregnancy and diabetes insipidus is unusual, and most cases are transient. In the present patient, it was considered that pre-existing subclinical partial diabetes insipidus became unmasked by pregnancy, although the exact mechanism remains unclear.

Key words Polyuria, Polydipsia, ADH, Pregnancy

Introduction

Diabetes insipidus is a rare cause of urinary frequency during pregnancy, with estimated rates ranging from 2 to 4 of every 100,000 pregnancies.[1] This condition has been tentatively classified as associated with pregnancy in patients with pre-existing diabetes insipidus, diabetes insipidus occurring during pregnancy, or diabetes insipidus occurring after delivery. Most of the cases belong to the second of those 3 conditions and are designated as transient diabetes insipidus during pregnancy (diabetes insipidus gravidarum). In the present report, we describe a patient with subclinical diabetes insipidus who developed transient central diabetes insipidus during pregnancy, along with a review of relevant literature.

Case Presentation

A 30-year-old woman was referred to our division because of polyuria and polydipsia. At the time of consultation, she was at 34 weeks of

*1 Division of Endocrinology and Metabolism, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya
Correspondence to: Yuji Moriwaki MD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. Tel: 81-798-45-6472, Fax: 81-798-45-6474, E-mail: moriwaki@hyo-med.ac.jp

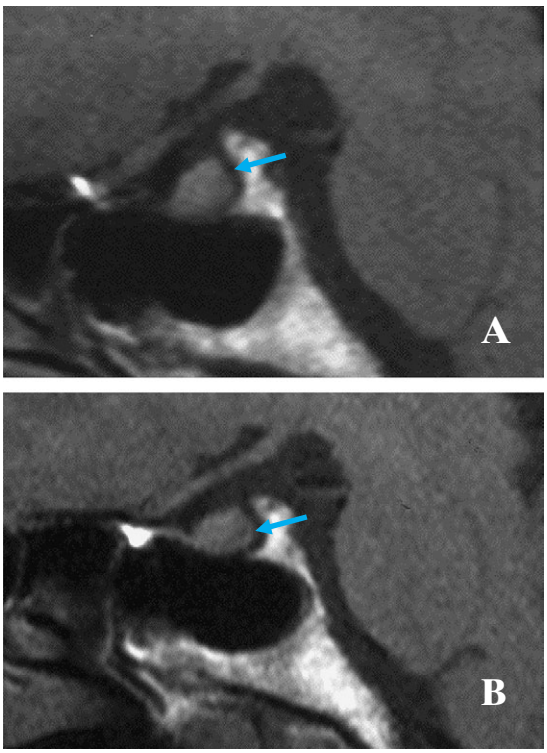

Fig. 1 Sagittal section of T_1-weighted MR-CT images of the pituitary gland before (A) and 4 months after (B) delivery

A high intensity signal from the posterior lobe is absent in both, suggesting persistent ADH depletion.

gestation and being followed by an obstetrician. Her family history and past history were not remarkable, though she had experienced mild polyuria during the first pregnancy. On examination, she was apparently in good health with a regular pulse rate of 114 beats per minute, a respiratory rate of 19 per minute, and blood pressure of 110/80 mmHg. Her height was 146 cm and her weight was 52.5 kg. There were no other abnormal findings in her chest, abdomen, and extremities, however, her urine output ranged from 5–8 L/day during hospitalization. A laboratory examination disclosed the following values: Total protein 6.9 g/dL, serum sodium 158 mmol/L, potassium 4.1 mmol/L, chloride 123 mmol/L, calcium 9.1 mg/dL, and serum and urine osmolality of 316 mOsm/L and 138 mOsm/L, respectively, suggesting hemoconcentration. The results of a liver function test were AST 50 U/L, ALT 34 U/L, LDH 302 U/L, and Alp 448 U/L. The fasting plasma glucose level was 123 mg/dL and urinalysis findings were normal. At 35 weeks of gestation, the patient showed polyuria and her basal plasma ADH value was 0.59 pg/mL, despite high plasma osmolality (292 mOsm/L). Intravenous hydration was started, however, neither a water-deprivation test nor salt challenge test was performed during pregnancy. MR-CT imaging of the pituitary gland did not show swelling of the pituitary gland or thickening of the pituitary stalk, however, there was evidence of disappearance of a high intensity signal in the posterior lobe in a T_1-weighted sequence, suggesting ADH depletion, although basal hormone secretion from the anterior pituitary gland was normal. A tentative diagnosis of central diabetes insipidus was made and she was given 1-desmino-8D-arginine-vasopressin (dDAVP) 2.5 μg twice intranasally, after which urine output decreased significantly and osmolality in serum and urine returned to normal ranges. At 39 weeks of gestation, the patient spontaneously gave birth to a 3,002 g male infant transvaginaly and the labor was uneventful. Following the birth, urine volume decreased spontaneously and dDAVP was discontinued without recurrence of polyuria. An 8-hour water-deprivation test, according to the modified method of Miller-Moses,[2] was performed 2 weeks after the delivery. After an overnight dehydration, an hourly urine collection was started, followed by 10 μg of intranasal dDAVP injection. After water deprivation, urine osmolality exceeded plasma osmolality, however, intranasal dDAVP administration increased urine osmolality by 17%. Thereafter, a hypertonic saline challenge test was performed 3 weeks after the delivery, during which 0.05 mL/kg/minute of 5% saline was infused for 2 hours. At the end of the test, plasma osmolality rose to 302 mOsm/L, however, ADH was only 2.66 pg/mL. These results are consistent with our earlier diagnosis of partial central diabetes mellitus. MR-CT imaging of the pituitary gland performed 4 months after delivery showed that the high intensity signal in the posterior lobe in a T_1-weighted sequence remained absent (Fig. 1). Therefore, a final diagnosis of subclinical incomplete central diabetes insipidus unmasked by pregnancy was made.

Discussion

Polyuria/pollakiuria during pregnancy is often

associated with excessive thirst due to a reduction in the thirst threshold, hyperglycemia, urinary tract infection, or compression of the urinary bladder by the enlarged uterus. The occurrence of diabetes insipidus with pregnancy is considered to be rare, with the incidence estimated to be from 2 to 4 of every 100,000 pregnancies,[1] but comparable with the estimated prevalence of 1:25,000 in the general population.[3] In the present patient, primary polydipsia was eliminated by the findings of increased serum osmolality and hypernatremia, while the response to intranasal dDAVP excluded nephrogenic diabetes insipidus. The present case was diagnosed with subclinical diabetes insipidus of the central type, which was not evident before pregnancy. During the previous pregnancy, she experienced similar symptoms, such as polyuria and polydipsia, thus, pregnancy might have been an aggravating factor for the development of overt central diabetes insipidus.

Although the causal linkage between diabetes insipidus and pregnancy remains unclear, several studies have speculated an underlying mechanism for this association.[4–6] Possible explanations include: 1) increased glomerular filtration, 2) increased vasopressinase activity,[7] 3) suppression of ADH secretion by swelling of the anterior lobe of the pituitary gland causing compression of the posterior lobe or by polydipsia due to a decreased thirst threshold,[8] 4) increased hepatic and renal clearance of ADH,[9] 5) hCG-induced reduction in osmotic threshold,[10] and 6) resistance to ADH,[9] possibly via increased renal prostaglandin production.[11,12] In the present case, swelling of the pituitary gland was not observed, however, other factors such as increased vasopressinase activity, increased prostaglandin concentration, increased hepatic and renal clearance of ADH, hCG-induced reduction in osmotic threshold, and diminished reactivity of the renal tubules to ADH during pregnancy may have contributed to expose the pre-existing subclinical diabetes insipidus.

Transient diabetes insipidus during pregnancy can be divided into that associated with pregnancy and that associated with another pre-existing disease. The former shows increased vasopressinase activity due to reduced degradation as a result of impaired liver function,[13] pre-eclampsia,[14] or unknown etiology,[7] thereby leading to transient diabetes insipidus, while the latter seems to be associated with a subclinical form of diabetes insipidus that becomes clinically evident only during pregnancy.[1,5,12,15,16] The MR-CT imaging and postpartum water deprivation and hypertonic saline challenge test findings, in which no polyuria was evident without dDAVP, indicated that the present case was subclinical diabetes insipidus of the central type, which was aggravated by pregnancy. In many patients with transient diabetes insipidus during pregnancy, MR-CT imaging and water deprivation testing is not performed after delivery, therefore the overall incidence of underlying subclinical diabetes insipidus may be underestimated.

For a diagnosis of diabetes insipidus during pregnancy, it is not recommended that a water-deprivation test be performed, since it will cause dehydration and hemoconcentration, leading to uteroplacental insufficiency that may be dangerous to both mother and fetus.[15] However, dDAVP should be administered as early as possible when the condition is suggested, since it does not possess oxytocic or pressor activities, and will not lead to premature delivery.[17] Moreover, since dDAVP does not appear in breast milk or possess teratogenic activity,[18] it is safe to use during and after pregnancy.[19]

In conclusion, the findings in the present case indicate that pregnancy may unmask subclinical diabetes insipidus. Therefore, patients who develop polyuria and/or polydipsia during pregnancy should be tested during the postpartum stage to detect latent diabetes insipidus, as the results will provide invaluable information for early diagnosis and treatment for polyuria during a subsequent pregnancy, as cases of recurrent diabetes insipidus during pregnancy have been described.[12,20]

References

1. Dürr JA, Lindheimer MD. Diagnosis and management of diabetes insipidus during pregnancy. Endocr Pract. 1996;2:353–361.
2. Miller M, Dalakos T, Moses AM, Fellerman H, Streeten DHP. Recognition of partial defects in antidiuretic hormone secretion. Ann Intern Med. 1970;73:721–729.

3. Baylis PH. Posterior pituitary. Hypothalamus and pituitary. In: Besser GM, Thorner MO ed. Comprehensive Clinical Endocrinology. 3rd ed. Mosby; 2002;85–102.
4. Hime MC, Richardson JA. Diabetes insipidus and pregnancy: Case report, incidence and review of literature. Obstet Gynecol Surv. 1978;33:375–379.
5. Baylis PH, Thompson C, Burd J, Tunbridge WMG, Snodgrass CA. Recurrent pregnancy-induced polyuria and thirst due to hypothalamic diabetes insipidus: An investigation into possible mechanisms responsible for polyuria. Clin Endocrinol (Oxf). 1986;24:459–466.
6. Davison JM, Gilmore EA, Durr J, Robertson GL, Lindheimer MD. Altered osmotic thresholds for vasopressin secretion and thirst in human pregnancy. Am J Physiol. 1984;246:F105–109.
7. Dürr JA, Hoggard JG, Hunt JM, Schrier RW. Diabetes insipidus in pregnancy associated with abnormally high circulating vasopressinase activity. N Engl J Med. 1987;316;1070–1074.
8. Davison JM, Shiells EA, Philips PR, Lindheimer MD. Serial evaluation of vasopressin release and thirst in pregnancy. Role of human chorionic gonadotropin in the osmoregulatory changes of gestation. J Clin Invest. 1988;81:798–806.
9. Davison JM, Sheills EA, Barron WM, Robinson AG, Lindheimer MD. Changes in the metabolic clearance of vasopressinase throughout human pregnancy. J Clin Invest. 1989;83:1313–1318.
10. Davison JM, Shiells EA, Philips PR, Lindheimer MD. Serial evaluation of vasopressin release and thirst in human pregnancy. Role of human chorionic gonadotropin in the osmoregulatory changes of gestation. J Clin Invest. 1988;81:798–806.
11. Bernheim J, Shapira J, David F, Behari C, Gelerntner I, Rathaus M. Renal prostaglandins E_2 and $F_{2\alpha}$ throughout normal human pregnancy. Eur J Clin Invest. 1986;16:113–116.
12. Williams DJ, Metcalfe KA, Skingle L, Stock AI, Beedham T, Monson JP. Pathophysiology of transient cranial diabetes insipidus during pregnancy. Clin Endocrinol (Oxf). 1993;38:595–600.
13. Cammu H, Velkeniers B, Charels K, Vinken W, Amy JJ. Idiopathic acute fatty liver of pregnancy associated with transient diabetes insipidus. Case report. Br J Obstet Gynaecol. 1987; 94:173–178.
14. Campbell DM, MacGillivary I, Carr-Hill R. Pre-eclampsia in second pregnancy. Br J Obstet Gynaecol. 1985;92:131–140.
15. Krege J, Katz VL, Bowes WA Jr. Transient diabetes insipidus of pregnancy. Obstet Gynecol Surv. 1989;44:789–795.
16. Iwasaki Y, Oiso Y, Kondo K, et al. Aggravation of subclinical diabetes insipidus during pregnancy. N Engl J Med. 1991;324: 522–526.
17. Robinson AG. DDAVP in the treatment of central diabetes insipidus. N Engl J Med. 1976;294:507–511.
18. Burrow GN, Wassenaar W, Robertson GL, Sehl H. DDAVP treatment of diabetes insipidus during pregnancy and the post-partum period. Acta Endocrinol. 1981;97:23–25.
19. Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. Obstet Gynecol Surv. 1998;53:450–455.
20. Hughes JM, Barron WM, Vance ML. Recurrent diabetes insipidus associated with pregnancy: pathophysiology and therapy. Obstet Gynecol. 1989;73:462–464.

COX-2 Inhibitors and the Risk of Cardiovascular Events

JMAJ 49(7・8): 276–278, 2006

Shuntaro Hara,*1 Ichiro Kudo*1

Key words COX-2, Cyclooxygenase, Prostaglandin, Prostacyclin, Thromboxane, Cardiovascular event

Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin demonstrate anti-inflammatory effects such as antipyretic or analgesic actions, by inhibiting cyclooxygenase (COX), a rate-limiting enzyme producing prostaglandin (PG), involved in fever and pain. It is known that there are two COX isozymes, designated as COX-1 and COX-2. However, while COX-1 is expressed constitutively in almost all organs, COX-2 is expressed in very limited fashion throughout most tissues unless induced by inflammatory stimuli or mitogens.[1] PGs not only exacerbate inflammation, but also have a significant effect on living organisms to protect gastric mucosa or adjust kidney function. COX-1 is thought to be related to the production of PGs, which have this protective effect on the gastrointestinal tract. However, classical NSAIDs inhibit not only COX-2, which in the inflammatory process acts to produce PGs thus causing fever and pain, but also inhibit COX-1, causing gastrointestinal tract disorders such as gastric ulcers. Hence, both domestic and international pharmaceutical companies launched the development of COX-2 selective inhibitors, hoping that if it is possible to isolate and inhibit COX-2, a new NSAID "Super aspirin" without adverse effects on the digestive system can be created. As a result, celecoxib (trade name: Celebrex), valdecoxib (trade name: Bextra) by Pfizer, rofecoxib (trade name: Vioxx) by Merck, and so forth were developed (Fig. 1).

Although COX-2 selective inhibitors were developed as anti-inflammatory drugs with less adverse effects, it was subsequently found to be effective in preventing the recurrence of cancer. In spite of it being known for some time from epidemiologic data that aspirin is effective in preventing recurrences of colon cancer, it became evident that COX-2 is excessively expressed not only in colon cancer tissues, but also in many other cancer tissues and that COX-2 inhibitors suppressed the occurrence and progression of cancer in animal models.[2] In response to these results, Merck and Pfizer carried out clinical trials to validate the effects of preventing the recurrence of colorectal adenoma in patients with a previous history of the disease. However, in the clinical trial, adenomatous polyp prevention on Vioxx study (APPROVe) by Merck, contrary to their expectations, it was revealed that rofecoxib increased the risk of cardiovascular disease.[3] After a year or more of treatment, differences in the occurrence of myocardial infarction and thrombotic apoplectic stroke gradually appeared between the placebo group and the rofecoxib group. After 18 months of treatment, with daily doses of 25 mg of rofecoxib, the rofecoxib group showed an increase in the risk of critical thromboembolic events, with a relative risk of 1.92, as compared to the placebo group. In response to these results, Merck in the United States immediately suspended the sales of this drug, which was making annual sales of 2,500 million US dollars as of September 2004 and ordered a recall. Furthermore, the clinical trials of rofecoxib in Japan, which were underway at the

*1 Department of Health Chemistry, School of Pharmaceutical Sciences, Showa University, Tokyo
Correspondence to: Shuntaro Hara PhD, Ichiro Kudo PhD, Department of Health Chemistry, School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan. Tel: 81-3-3784-8196, Fax: 81-3-3784-8245, E-mail: kudo@pharm.showa-u.ac.jp

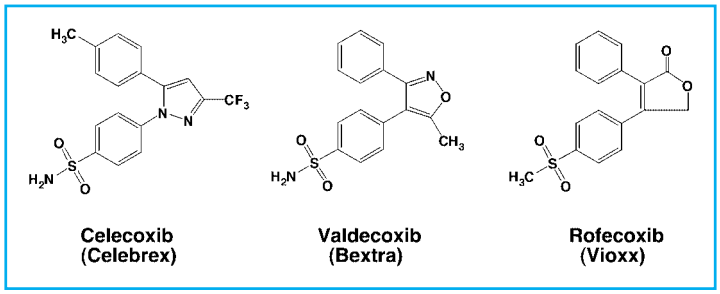

Fig. 1 Chemical structures of COX-2 selective inhibitors

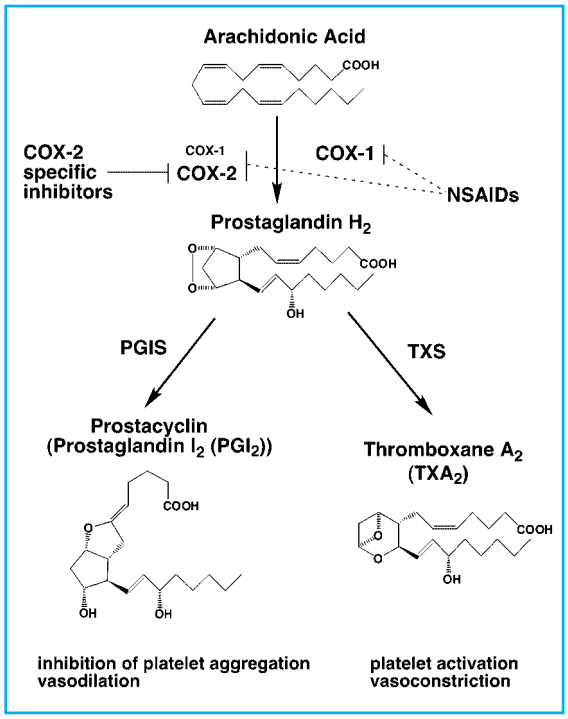

Fig. 2 Biosynthetic pathways of PGI_2 and TXA_2
PGIS, prostacylin synthase; TXS, thromboxane synthase

time, were discontinued.

In fact, the risk of rofecoxib was expected to some extent in the VIGOR trial (Vioxx Gastrointestinal Outcomes Research), which evaluated its effects on the gastrointestinal tract.[4] This research, which compared rofecoxib with the classical NSAID, naproxen, indicated that the risk of occurrences of gastrointestinal tract disorders was half with rofecoxib, although the occurrence of myocardial infarction was in turn 5 times more. However, at that time, it was insisted that naproxen had cardioprotective effects.

On the other hand, in a long-term trial studying the effects of celecoxib on cancer patients, Pfizer reported no increase of cardiovascular risk. COX-2 selective inhibitors are classified into sulfones and sulfoamides. Rofecoxib is a sulfone, while celecoxib and valdecoxib are sulfonamides (Fig. 1). Sulfone COX-2 inhibitors promote oxidization of lipoprotein, unlike sulfonamide COX-2 inhibitors. Based on their different constitutions, COX-2 inhibitors are reported to have different effects in increasing the risk of cardiovascular diseases.[5] However, in the APC trial (adenoma prevention with celecoxib) by the National Cancer Institute, the results differed from those of the report by Pfizer. A daily celecoxib dose of 400 mg also increased the risk of cardiovascular diseases 3.4 times.[6] Although there are differences in their effects, almost all of COX-2 inhibitors increase the risk of cardiovascular disease.

Currently, the mechanism with which COX-2 inhibitors increase cardiovascular risk is thought to be attributed to the break-down of the production balance of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2).[7] Although TXA_2 and PGI_2 are both produced by COX, they demonstrate totally opposite effects (Fig. 2). TXA_2, which has vasoconstrictive and platelet-aggregating effects, is produced by COX-1 from platelets. On the other hand, PGI_2, which has vasodilatory effects and inhibits platelet aggregation, is produced from vascular endothelial cells. In vascular endothelial cells, PGI_2 is also produced by COX-1, but in many cases, COX-2 is synthesized in response to extracellular stimulus, for instance, in accordance to the alteration of blood flow from variation in blood pressure, producing PGI_2. In our

bodies, the production balance of TXA_2, which is produced by COX-1 in the platelets, and PGI_2, which is produced by COX-2 in vascular endothelial cells, is kept steady and blood flow and clot formation are adjusted. Since classical NSAIDs inhibit both COX-1 and COX-2, it does not upset this balance. However, it is thought that when a drug which inhibits COX-2 only is used, while TXA_2 in platelets remains unaffected, PGI_2 synthesis in vascular endothelial cells is inhibited, resulting in an increase in platelet aggregation and the risk of cardiovascular diseases such as atherosclerosis or thrombosis. For this reason, although rofecoxib demonstrates higher selectivity than celecoxib, some researchers think that inhibitors with a high specificity against COX-2 may indicate prominent increase in the risk of cardiovascular diseases.

Although the use of rofecoxib has been discontinued, other COX-2 inhibitors are still on the market. Furthermore, some companies are still developing drugs which have COX-2 inhibitory effects. It is true that COX-2 has merits without adverse effects of gastrointestinal tract disorders. For the future, it is deemed important to recognize the increased risk of cardiovascular diseases with COX-2 inhibitors and use these drugs properly by not administering them to patients with cardiovascular diseases like ischemic heart disease.

References

1. Turini ME, DuBois RN. Cyclooxygenase-2: a therapeutic target. Annu Rev Med. 2002;53:35–57.
2. Marnett LJ, DuBois RN. COX-2: a target for colon cancer prevention. Annu Rev Pharmacol Toxicol. 2002;42:55–80.
3. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092–1102.
4. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520–1528.
5. Walter MF, Jacob RF, Day CA, Dahlborg R, Weng Y, Mason RP. Sulfone COX-2 inhibitors increase susceptibility of human LDL and plasma to oxidative modification: comparison to sulfonamide COX-2 inhibitors and NSAIDs. Atherosclerosis. 2004;177:235–243.
6. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352:1071–1080.
7. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med. 2004;351:1709–1711.

Internet Addiction among Students: Prevalence and psychological problems in Japan

JMAJ 49(7・8): 279–283, 2006

Takeshi Sato*1

Key words Internet addiction, Diagnostic criteria, Prevalence, Psychological problem

The explosive growth of the Internet in the last decade has had a huge impact on communication and interpersonal behavior. Psychological research during the same period has sought to increase understanding of this impact. The Internet was originally designed to facilitate communication and research activities. However, the dramatic increase in the use of the Internet in recent years has led to pathological use (Internet addiction). The effect of Internet addiction includes the impairment of academic performance, psychological well-being, and interaction with peers and family members.

To understand the current status in Japan, this study reviews the prevalence of Internet addiction among students and compares it with that in foreign countries. It also introduces psychological problems concerned with Internet addiction and mobile phone E-mail encountered in a primary care practice.

Definition of Internet Addiction

Addictive use of the internet is a new phenomenon that many practitioners are unaware of and consequently unprepared to treat. Some practitioners are unfamiliar with the Internet, making its seductive powers difficult to understand. Sometimes its impact on the afflicted person's life is underestimated as many practitioners do not recognize the legitimacy of the disorder. Hence, this paper starts with a review of the diagnostic criteria of internet addiction to help prepare clinicians for this issue.

The best method clinically to detect compulsive use of the internet is to compare it with criteria for other established addictions. Of all the diagnoses referenced in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[1] pathological gambling was viewed as most akin to this phenomenon. Prior research defined internet addiction as an impulse control disorder that does not entail an intoxicant.

Using pathological gambling as a model, Young[2] developed eight items of criteria of Internet dependency that modified the DSM-IV criteria to be used as a screening device to differentiate "dependent" from "non-dependent" users. The questions are shown in Table 1.

Patients are considered "addicted" when answering "yes" to five or more of the questions and when their behavior cannot be better accounted for by a manic episode. The cut off score of "five" is consistent with the number of criteria used for pathological gambling and seen as an adequate number of criteria to differentiate normal from pathological internet use.

Official criteria for the diagnosis of Internet Addiction Disorder (IAD) along with more information on IAD and subscription information for the Internet Addiction Support Group (IASG) are available on Ivan Goldberg's website.[3]

Screening Devices for Internet Addiction

How do patients know if they are already addicted

*1 Health Care Center, Saga University, Saga
Correspondence to: Takeshi Sato MD, PhD, Health Care Center, Saga University, 1-Honjo, Saga, Saga 840-8502, Japan.
Tel: 81-952-28-8181, Fax: 81-952-28-8184, E-mail: satot@cc.saga-u.ac.jp

Table 1 Diagnostic criteria for Internet addiction according to DSM-IV[2]

1. Do you feel preoccupied with the Internet (think about previous on-line activity or anticipate the next on-line session)?
2. Do you feel the need to use the Internet with increasing amounts of time in order to achieve satisfaction?
3. Have you repeatedly made unsuccessful efforts to control, cut back, or stop Internet use?
4. Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop Internet use?
5. Do you stay on-line longer than originally intended?
6. Have you jeopardized or risked the loss of a significant relationship, job, educational or career opportunity because of the Internet?
7. Have you lied to family members, therapist, or others to conceal the extent of your involvement with the Internet?
8. Do you use the Internet as a way of escaping from problems or of relieving a dysphoric mood (for example, feelings of helplessness, guilt, anxiety, depression)?

Table 2 Internet Addiction Test (IAT)[2]

To assess level of addiction, answer the following questions using this scale: 1=Rarely, 2=Occasionally, 3=Frequently, 4=Often, 5=Always.
1. How often do you find that you stay on-line longer than you intended?
2. How often do you neglect household chores to spend more time on-line?
3. How often do you prefer the excitement of the Internet to intimacy with your partner?
4. How often do you form new relationships with fellow on-line users?
5. How often do others in your life complain to you about the amount of time you spend on-line?
6. How often do your grades or school work suffer because of the amount of time you spend on-line?
7. How often do you check your e-mail before something else that you need to do?
8. How often does your job performance or productivity suffer because of the Internet?
9. How often do you become defensive or secretive when anyone asks you what you do on-line?
10. How often do you block out disturbing thoughts about your life with soothing thoughts of the Internet?
11. How often do you find yourself anticipating when you will go on-line again?
12. How often do you fear that life without the Internet would be boring, empty, and joyless?
13. How often do you snap, yell, or act annoyed if someone bothers you while you are on-line?
14. How often do you lose sleep due to late-night log-ins?
15. How often do you feel preoccupied with the Internet when off-line, or fantasize about being on-line?
16. How often do you find yourself saying “just a few more minutes” when on-line?
17. How often do you try to cut down the amount of time you spend on-line and fail?
18. How often do you try to hide how long you’ve been on-line?
19. How often do you choose to spend more time on-line over going out with others?
20. How often do you feel depressed, moody, or nervous when you are off-line, which goes away once you are back on-line?

Table 3 Prevalence of Internet addiction among students

Year	Authors	Country	Subjects	Number of Subjects	Percentage of Internet Addiction	Assessment Tool
1997	Scherer[5]	South America	college	531	13.0	Internet dependence
2000	Chou & Hsiao[6]	Taiwan	college	910	5.9	IAS
2000	Morahan-Martin & Schumacher[4]	US	college	283	8.1	PIU scale
2001	Anderson[7]	US	college	1,300	9.8	Internet dependence
2001	Wang[8]	Australia	college	293	9.6	IAD
2002	Mingyi[9]	China	college	500	6.4	IAD
2002	Lin & Tsai[10]	Taiwan	high school	753	11.7	Chinese IAS
2004	Johansson & Gotestam[11]	Norway	12–18 years	3,237	10.7	IAS 40 or more
2004	Sato[12]	Japan	college	242	9.1	IAS 40 or more
2005	Niemz et al.[13]	UK	college	371	18.3	PIU scale
2006	Kim et al.[14]	Korea	high school	1,573	39.6	IAS 40 or more

(IAS: Internet Addiction Scale; PIU: Pathological Internet Use; IAD: Internet Addiction Disorder)

or rapidly tumbling toward trouble? Everyone's situation is different, and it's not simply a matter of time spent on-line. Some patients feel they are addicted with only twenty hours of Internet use, while others who spent forty hours on-line insist it is not a problem to them. It's more important to measure the damage their Internet use causes in their life. What conflicts have emerged in family, relationships, work, or school?

The Internet Addiction Test (IAT) developed by Young[2] appears in his book, *Caught in the Net*. This is a simple exercise that helps people in two ways: 1) If patients already know or strongly believe they are addicted to the Internet, this guide will assist them in identifying the areas in their life most impacted by their excessive Net use; and 2) If they are not sure whether they are addicted or not, this will help determine the answer and begin to assess the damage done. When answering, respondents should only consider the time they spent on-line for non-academic or non-job related purposes. The IAT has been already translated into Japanese and can be used by clinicians for screening in their clinic if they want to rule out Internet addiction (Table 2). After patients have answered all the questions, add the numbers they selected for each response to obtain a final score. The higher their score, the greater their level of addiction and the greater the number of problems their Internet usage causes. Here's a general scale to help measure their score:

20–49 points: You are an average on-line user. You may surf the Web a bit too long at times, but you have control over your usage.

50–79 points: You are experiencing occasional or frequent problems because of the Internet. You should consider its full impact on your life.

80–100 points: Your Internet usage is causing significant problems in your life. You should evaluate the impact of the Internet on your life and address the problems directly caused by your Internet usage.

Another scale includes Pathological Internet Use Scale (PIUS) developed by Morahan-Martin and Schumacher.[4]

Prevalence of Internet Addiction

The prevalence of Internet addiction is shown in Table 3. These studies were undertaken using varying instruments, and show that 8–10% of college students have Internet dependence.[4–14] These results were obtained from many college student

Table 4 Gender difference in addiction[15]

Addiction	Gender Difference	Addiction	Gender Difference
Substances		**Activities**	
Alcohol	M>W	Exercise	M=W
Cigarettes	M>W	Television	M=W
Caffeine	M<W	Internet use	M>W
Chocolate	M<W	Video games	M>W
		Gambling	M>W

population studies and are similar to results in Japan, but primary care physicians may also need data based on community samples.

It is difficult to predict the future prospects of Internet dependence. It might be on the increase, or it may fade out. Before drawing any conclusions about this, it is necessary to perform a prevalence study of Internet addiction on a large scale in Japan. Case studies of Internet addicts may also provide more insight into the specific nature of the disorder.

Characteristics of Internet Addiction

With regard to gender and addiction, Greenberg et al.[15] reported an interesting pattern of gender differences in addictive tendencies (Table 4). Analyses on the individual substances and activities revealed that men reported greater level of addiction to cigarettes, alcohol, video games, gambling, and internet use. On the other hand, women reported greater levels of addiction to chocolate and caffeine. No significant differences were found for exercise or television. Men tend to be addicted to the Internet.

Furthermore, low self-esteem has been linked to addictive behaviors. Armstrong et al. investigated whether low self-esteem was associated with Internet addiction, and found that self-esteem was a good predictor of Internet addiction and amount of time spent on-line per week. According to Kim et al. [14] the level of depression and suicidal ideation were highest in the Internet-addicts group. Further studies should investigate the direct relationship between psychological health problems and Internet dependence.

Future Problems of Internet Addiction in Japan

Recently, the use of E-mail on mobile phones among adolescents in Japan has been increasing. New and serious psychological problems have arisen relative to the spread of mobile phones. Some Japanese adolescents with school refusal use the mobile phone E-mail to communicate with their friends excessively. I encountered two cases of high school students with school refusal in a primary care practice. They sent E-mail to their friends more than 200 times a day. They could not stop using mobile phone E-mail, and then were exhausted from sending mail all day, which resulted in depression. They had developed addictive and compulsive behavior to E-mail use on mobile phones, which impaired their academic performance, psychological well-being, and interpersonal relationships with friends and family members.

As shown in the case vignettes of these two high school students, new psychological problems have developed as a result of the change of communication media in Japan. We should pay more attention to adolescents' feelings and then propose possible solutions for problematic behavior among students.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of the Mental Disorders, 4th ed. Washington DC: American Psychiatric Publishing, Inc.; 1994.
2. Young KS. Caught in the Net: How to Recognize the Sign of Internet Addiction and a Winning Strategy for Recovery. New York: John Wiley & Sons; 1996. (Odashima Y. Mainichi Publishing Co.; 1998, translated in Japanese)
3. Goldberg I. Internet Addictive Disorder (IAD) Diagnostic Criteria. Available on line at http://www.psycom.net/iadcriteria.html
4. Morahan-Martin J, Schumacher P. Incidences and correlates of pathological Internet use among college students. Computers in Human Behavior. 2000;16:13–29.
5. Schere K. College life on-line: healthy and unhealthy Internet use. J of College Student Development. 1997;38:655–665.
6. Chou C, Hsiao MC. Internet addiction, usage, gratification, and pleasure experience: The Taiwan college students' case. Computers and Education. 2000;35:65–80.
7. Anderson KJ. Internet use among college students: an exploratory study. J Am Coll Health. 2001;50:21–26.
8. Wang W. Internet dependency and psychosocial maturity among college students. Int J Hum Comp. 2001;55:919–938.
9. Mingyi Q. Internet abuse raises concern. Available on line at http://www.china.org.cn/english/25467.htm
10. Lin SSJ, Tsai CC. Sensation seeking and Internet dependence

of Taiwanese high school adolescents. Comput Hum Bahav. 2002;18:411–426.
11. Johansson A, Gotestam K. Internet addiction: Characteristics of a questionnaire and prevalence in Norwegian youth (12–18 years). Scand J Psychol. 2004;45:223–229.
12. Sato T. Psychiatric consultation in the Internet addiction. Jpn J Psychiat. 2004;9:345–351. (in Japanese)
13. Niemz K, Griffiths M, Banyard P. Prevalence of pathological Internet use among university students and correlations with self-esteem, the General Health Questionnaire (GHQ), and Disinhibition. Cyberpsychol Bahav. 2005;8:562–570.
14. Kim K, Ryu E, Chon MY, et al. Internet addiction in Korean adolescents and its relation to depression and suicidal ideation: A questionnaire survey. Int J Nurs Stud. 2006;43:185–192.
15. Greenberg JL, Lewis SE, Dodd DK. Overlapping addictions and self-esteem among college men and women. Addict Behav. 1999;24:565–571.