Discussion

EEG recording from the scalp is widely used as a non-invasive electrophysiological recording method. In order to assess cognitive dysfunction, investigation of event-related potential (ERP), P300, could be a first choice [5]. Aging is one of the major risk factors that lead to cognitive dysfunction, and, indeed, the latency of ERP P300 tends to prolong as aging advances [2, 4]. In the case of Alzheimer disease (AD) patients, the peak latency of ERP P300 tends to be further prolonged compared to normal aging [12]. Thus, the P300 recording method has been developed as a diagnostic method.

Another method under development for assessment of cognitive dysfunctions is source analysis of EEG frequency. Previous studies reported that theta activities are increased and beta activities are decreased in AD patients when compared to controls [3, 8, 13]. Recently, it has been reported that sources of delta and alpha frequency bands differ in MCI and AD [1]. In those studies, EEG recordings were performed in the awake condition with the eyes closed. It was based on source analysis by dipole-fitting from multiple point data on the scalp.

In the present study, our attention is focused on less invasive and less stressful methods by EEG recording from the frontal area of the scalp. By comparing EEG rhythms evoked by different sensory stimulation, we successfully demonstrated that variations of rhythm patterns decrease in dementia patients as compared with healthy controls, and that a decrease in cognitive function might be related to a decrease in the ability to generate various cortical rhythm patterns. However, we must consider influences of aging on the decrease in variations of rhythm patterns, since normal healthy controls were recruited from a younger age group as well as older age group. In the case of alpha2 frequency bands, there is a negative correlation between variation score and age ($R = -0.44$, $P = 0.025$), when the level of significance is 0.05. Indeed, this suggests that aging also influences a decrease in variations of rhythm patterns in the alpha2 frequency band. But the influence of age seems mild, since there is no correlation when the level of significance is 0.01, and the P value between variation score and age ($R = -0.44$, $P = 0.025$) is much higher compared with that between the variation score and HDS-R ($R = -0.88$, $P < 0.0001$). In the cases of the theta and beta frequency bands, there is no correlation between variation score and age ($R = 0.23$, $P = 0.26$ and $R = 0.27$, $P = 0.19$, respectively). In the case of the alpha3 frequency band, there is a negative correlation between variation score and age ($R = -0.56$, $P = 0.003$), but there is no correlation between variation score and HDR-S ($R = 0.48$, $P = 0.13$), when the level of significance is 0.01. Thus, these findings suggest that influences of aging on a decrease in variations of rhythm patterns are relatively small.

Since EEGs were recorded from the frontal cortex only, the present data did not reflect whole brain activities, but the significance was that differences of electrophysiological activities between dementia patients and healthy controls were detected. Moreover, the present results suggest that a decrease in cognitive function might be correlated with a decrease in variations of cortical rhythm patterns between the different tasks. Combining the electrophysiological and psychometric examination, as we have shown in this study, might enable us to assess cognitive dysfunction comprehensively, and might be useful as diagnostic criteria of early-stage dementia.

Acknowledgments We wish to thank Mr. H. Adachi and Mr. S. Muramoto for technical assistance. This work was supported by grants from the Ministry of Health, Labor and Welfare of Japan (Comprehensive Research on Aging and Health, H-17-Chouju-018), the Japan Health Foundation, the Ministry of Education, Culture, Sports, Science, and Technology (Grant-in-Aid for Scientific Research C 22590966), High-Tech Research Center of Kanazawa Medical University (H2008, 2009, 2010-13, 14), and the Scientific Research Promotion Fund of the Promotion and Mutual Aid Corporation for Private Schools of Japan.

References

1. Babiloni C, Binetti G, Cassetta E, Forno GD, Percio CD, Ferreri F, Ferri R, Frisoni G, Hirata K, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Rodriguez G, Romani GL, Salinari S, Rossini PM (2006) Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study. Clin Neurol 117:252–268
2. Barrett G, Neshige R, Shibasaki H (1987) Human auditory and somatosensory event-related potentials: effects of response condition and age. Electroencephalogr Clin Neurophysiol 66:409–419
3. Dierks T, Perisic I, Frolich L, Ihl R, Maurer K (1991) Topography of the quantitative electroencephalogram in dementia of the Alzheimer type. Electroenceph Clin Neurophysiol 55:372–380
4. Dujardin K, Derambre P, Bourriez JL, Jacquesson JM, Guieu JD (1993) P300 component of the event-related potentials (ERP) during an attention task: effect of age, stimulus modality and event probability. Int J Psycophysiol 14:255–267
5. Duncan-Johnson CC, Donchin E (1982) The P300 component of the event-related brain potential as an index of information processing. Biol Psychol 14:1–52
6. Huang C, Wahlund L-O, Dieks T, Julin P, Winblad B, Jelic V (2000) Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG source: a cross-sectional and longitudinal study. Clin Neurol 111:1961–1967
7. Jagust W, Reed B, Mungas D, Ellis W, Decarli C (2007) What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? Neurology 69:871–877
8. Jelic V, Shigeta M, Julin P, Winblad O, Wahlund LO (1996) Quantitative electroencephalography power and coherence in Alzheimer disease and mild cognitive impairment. Dementia 7:314–323

9. Morris JC, Mckeel DW, Storand M (1991) Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. Neurology 41:469–478
10. Ohnishi T, Matsuda H, Tabira T, Asada T, Uno M (2001) Changes in brain morphology in Alzheimer disease and normal aging: is Alzheimer disease an exaggerated aging process? Am J Neuroladiol 22:1680–1685
11. Peterson RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. Arch Neurol 58:1985–1992
12. Polich J, Corey-Bloom J (2005) Alzheimer's disease and P300: review and evaluation of task and modality. Curr Alzheimer Res 2:515–525
13. Prinz PN, Vitiello MV (1989) Dominant occipital (alpha) rhythm frequency in early stage Alzheimer's disease and dementia. Electroencephalogr Clin Neurophysiol 73:427–432
14. Tierney MC, Szalai JP, Snow WG, Fisher RH, Nores A, Nadon G, Dunn E, St George-Hyslop PH (1996) Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. Neurology 46:661–665

J Bone Miner Metab (2011) 29:37–43
DOI 10.1007/s00774-010-0188-x

ORIGINAL ARTICLE

Design of a pragmatic approach to evaluate the effectiveness of concurrent treatment for the prevention of osteoporotic fractures

Rationale, aims and organization of a Japanese Osteoporosis Intervention Trial (JOINT) initiated by the Research Group of Adequate Treatment of Osteoporosis (A-TOP)

Masataka Shiraki · Tatsuhiko Kuroda · Nobuaki Miyakawa · Naohito Fujinawa · Kazumasa Tanzawa · Akiko Ishizuka · Shiro Tanaka · Yukari Tanaka · Takayuki Hosoi · Eiji Itoi · Shigeto Morimoto · Akira Itabashi · Toshitsugu Sugimoto · Toshihiko Yamashita · Itsuo Gorai · Satoshi Mori · Hideaki Kishimoto · Hideki Mizunuma · Naoto Endo · Yoshiki Nishizawa · Kunio Takaoka · Yasuo Ohashi · Hiroaki Ohta · Masao Fukunaga · Toshitaka Nakamura · Hajime Orimo

Received: 27 November 2009 / Accepted: 23 March 2010 / Published online: 13 May 2010

Abstract The aim of osteoporosis treatment is to prevent future fractures. Although concurrent treatment has been used very frequently for osteoporosis in clinical practice, there are no data on accurate and verified effectiveness of concurrent treatment for fracture prevention in patients with osteoporosis. To clarify the clinical usefulness of concurrent treatment, the Japan Osteoporosis Society has authorized the establishment of the A-TOP (Adequate Treatment of Osteoporosis) research group. The objective of this research is to establish a design for a clinical trial to prove whether concurrent treatment using both alfacalcidol (1-alpha-hydroxycholecalciferol) and alendronate is more effective as compared to treatment using alendronate alone

For the A-TOP (Adequate Treatment of Osteoporosis) Research Group.

M. Shiraki (✉)
Department of Internal Medicine, Research Institute and Practice for Involutional Diseases, 1610-1 Meisei, Misato, Azumino, Nagano 399-8101, Japan
e-mail: ripid@fc4.so-net.ne.jp

T. Kuroda · N. Miyakawa
Public Health Research Foundation, Tokyo, Japan

N. Fujinawa
I'cros Co., Ltd., Tokyo, Japan

K. Tanzawa
ING Corporation, Tokyo, Japan

A. Ishizuka
Japan Clinical Research Support Unit, Tokyo, Japan

S. Tanaka
Division of Clinical Trial Design and Management, Translational Research Center, Kyoto University, Kyoto, Japan

Y. Tanaka
Department of Epidemiology and Biostatistics, School of Health Sciences and Nursing, The University of Tokyo, Tokyo, Japan

T. Hosoi
Department of Advanced Medicine, National Center for Geriatrics and Gerontology, Aichi, Japan

E. Itoi
Department of Orthopaedic Surgery, Tohoku University School of Medicine, Sendai, Japan

S. Morimoto
Geriatric Medicine, Kanazawa Medical University, Ishikawa, Japan

A. Itabashi
Saitama Center for Bone Research, Kubojima Clinic, Saitama, Japan

T. Sugimoto
Department of Endocrinology and Metabolism, Faculty of Medicine, Shimane University, Shimane, Japan

T. Yamashita
Department of Orthopaedic Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan

I. Gorai
Department of Obstetrics and Gynecology, International University of Health and Welfare Atami Hospital, Shizuoka, Japan

S. Mori
Bone and Joint Surgery, Seirei Hamamatsu General Hospital, Shizuoka, Japan

in terms of fracture prevention. The present study was named JOINT (Japanese Osteoporosis Intervention Trial) and is based on a method using national, prospective, randomized, open-labeled, blinded endpoints focusing on postmenopausal osteoporosis with a high risk for fracture. The patients were mainly selected by practitioners and allocated randomly by a central registration system into two groups, of which one received 5 mg/day of alendronate alone, and the other received 1 μg/day of 1-alpha-hydroxycholecalciferol (alfacalcidol) in addition to the alendronate. The endpoints focused primarily on fracture prevention, and the patients' quality of life (QOL) and change in body height, as well as adherence and the adverse events of the treatments were evaluated secondarily. To obtain sufficient statistical power in the events during a 2-year observation period, the patients who are expected to have higher risk were selected to participate in this study, and it was decided that the final plan would involve 890 patients per group (two-sided alpha = 0.05, power = 0.8). Data collection began in November 2003. Correspondence regarding the registration of the investigator and the progress of the study was conducted through a web system from the Public Health Research Foundation to practitioners.

Keywords Alendronate · Alfacalcidol · Concurrent treatment · Fracture prevention · Osteoporosis

Introduction

Osteoporosis, which is characterized by compromised bone strength and increased susceptibility to fractures, which lead to deterioration in the QOL and increased mortality, is a national burden on an aging society [1, 2]. However, recent studies indicate that treatment with a parathyroid hormone, bisphosphonates or a selective estrogen receptor modulator (SERM) [3–9] may decrease the risk of fractures in patients with osteoporosis.

Although bisphosphonate treatment currently represents the most powerful form of treatment available for fracture prevention in osteoporotic patients, it has not succeeded in completely preventing osteoporotic fractures [3–5, 7–9]. Therefore, concurrent treatment of osteoporosis has been frequently used by Japanese practitioners without any concrete evidence regarding fracture reduction. Since the concept of evidence-based medicine (EBM) has been introduced to clinical practice since the 1990s [10], the Japan Osteoporosis Society and the Japanese Society of Bone Mineral Research have edited the clinical guideline for treatment of osteoporosis (Chief editor: Hajime Orimo [11]). However, the writers recognized that there was a lack of evidence in the effectiveness of concurrent treatment of osteoporosis. Furthermore, it was expected that the patients who visit clinics have varying degrees of risk of fracture, which may differ from the degree of those who participated in development trials for bisphosphonates. This possibility would make it easier to obtain pragmatic evidence in general clinical practice.

Starting in 2000, the Japan Osteoporosis Society had planned to investigate the effectiveness of treatment of osteoporosis in order to provide evidence to general practitioners. Before constructing evidence, some feasibility studies were required to confirm the consensus in the diagnosis of incident fractures among the researchers and to elucidate the risk of future fractures in the patient population. In addition to these efforts in the field of osteoporosis, the Japanese government also established an

H. Kishimoto
Department of Orthopedic Surgery, San-in Rosai Hospital, Tottori, Japan

H. Mizunuma
Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Aomori, Japan

N. Endo
Division of Orthopedic Surgery, Niigata University Medical and Dental Hospital, Niigata, Japan

Y. Nishizawa
Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

K. Takaoka
Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, Japan

H. Ohta
Department of Obstetric and Gynecology, Tokyo Women's Medical University, Tokyo, Japan

M. Fukunaga
Department of Nuclear Medicine, Kawasaki Medical School, Okayama, Japan

T. Nakamura
Department of Orthopedic Surgery, University of Occupational and Environmental Health School of Medicine, Kokura, Japan

H. Orimo
Health Science University, Yamanashi, Japan

ethical guideline for clinical trials [12], and the International Committee of Medical Journal Editors launched a clinical trial registry [13]. Such kinds of progress in the circumstances of clinical trials have enabled for investigator-initiated clinical trials in general practice.

The Adequate Treatment of Osteoporosis (A-TOP) study group was established in 2000 [11] in affiliation with the Japan Osteoporosis Society and organized a team for clinical trial management. The team consisted of clinical investigators (planning and analysis), foundation (funding) managers, officers from non-profit organization (data management) and several companies (data collection). This was the first joint team to create the post-making evidence for osteoporosis. In November 2003, A-TOP initiated a randomized clinical trial referred to as the Japanese Osteoporosis Intervention Trial (JOINT). The purpose of JOINT was to confirm the clinical significance of concurrent use of osteoporotic drugs. The first protocol, named JOINT-01, was initiated in 2002, but was suspended the following year due to a change in drug labeling. A second protocol, named JOINT-02, was established to clarify the effect of adding 1-alpha-hydroxycholecalciferol (alfacalcidol) to alendronate (ALN), using the incident fracture rate as the primary endpoint. In this paper, the rationale, organization and study design of JOINT-02 are introduced.

Rationale and aims

In 2002, the Japan Society of Osteoporosis sent a letter to randomly selected practitioners and enclosed a questionnaire regarding whether concurrent treatment using bisphosphonate and another drug was being utilized to treat osteoporosis. Surprisingly, 87.8% (79/90 practitioner) of the doctors who responded did have experience using concurrent treatment [14]. The most frequent drugs used in concurrent treatment with amino-bisphosphonate were alfacalcidol (93.7%), followed by calcitonin (50.6%), as there were expectations for these drugs to exhibit more potent inhibition of fracture occurrence or more significant increase in BMD, even though there was no apparent evidence. In addition to the lack of evidence related to fracture prevention, the safety profile of concurrent treatment had not been evaluated. Thus, evaluations of the effectiveness and safety of concurrent treatment were urgently required. Etidronate [15] and ALN [8, 9] were used as the drugs to confirm anti-fracture effectiveness in comparison to alfacalcidol in Japanese osteoporotic patients. However, these clinical trials were carried out at specific institutions and were initiated by experts in accordance with tight regulations. As a result, there may have been differences in the selected treatment and in the backgrounds of the patients between treatments conducted at these institutions and those conducted in general practice. In addition, the adherence of the treatment is expected to be lower in general practice than in institutions with experts who are committed to developmental trials. Thus, pragmatic study is urgently needed to evaluate whether bisphosphonates are effective to the same extent at the level of general practitioners as compared to the prior study (Phase III study).

Feasibility studies

The Japan Osteoporosis Society started discussions to execute a national clinical trial for obtaining evidence regarding the effectiveness of concurrent treatment in 2000. An executive committee of A-TOP was organized in 2002 and planned on forming a consensus regarding judgment standards for pre-existing fractures and incident vertebral fractures [16]. Morphometric criteria for incident fractures combined with a semi-quantitative assessment were thought to provide useful information on the study of clinical osteoporosis, especially for international comparisons. Next, to assume the number of participants in the clinical trial, the incident fracture rate and the risk of incident fracture were analyzed in the patient population, and the number of participants with sufficient statistical power [17] was calculated. Bone resorption marker was an independent risk factor for incident vertebral fractures in Japanese women. When the newly discovered risk factor was incorporated into the inclusion criteria in addition to conventional selection criteria such as age, prevalent fractures and bone mineral density, a reduction of about 40% in the estimated sample size was achieved. Thus, measurement of bone resorption markers is useful in reducing the sample size and the observation period in fracture-prevention studies carried out for developing drugs used to treat osteoporosis.

Materials and methods

Study design

Objective

JOINT was the first national, prospective, randomized, multicenter, open-labeled, blinded endpoints, controlled trial for osteoporosis made up mainly of practitioners of investigators in Japan. The objective of JOINT-02 was to clarify additive efficacy in terms of fracture prevention and safety, QOL and adherence in simultaneous use of alfacalcidol and ALN.

Subjects, intervention and endpoints

Confirmations regarding the patients were made by practitioners based on the inclusion and exclusion criteria (Table 1) after obtaining written informed consent. The

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Postmenopausal osteoporosis[a]
Over 70 years old
Ambulatory patients who do not require any help
Able to answer QOL questionnaire
Corresponds to more than one of A-TOP's risk factors for fracture[b]
Exclusion criteria
Metabolic bone diseases other than osteoporosis[c]
Contraindication to the drugs (ALN or alfacalcidol)
Dysfunction in communication of intentions
Severe degenerative deformation of vertebra
Abnormal heart function
Abnormal hepatic function
Abnormal kidney function
Treatment of osteoporosis by bisphosphonate within 6 months prior to the present study

These thresholds were decided by risk analysis by the A-TOP research group

[a] Over 1 year after menopause

[b] Pre-existing vertebral fracture number ≥ 1; BMD $\leq$ Young Adult Mean -3 SD; Urinary DPD ≥ 7.6 nmol/mmol Cr; or NTX $\geq$ 54.3 nmol BCE/mmol Cr

[c] Hyperparathyroidism and hyperthyroidism were excluded

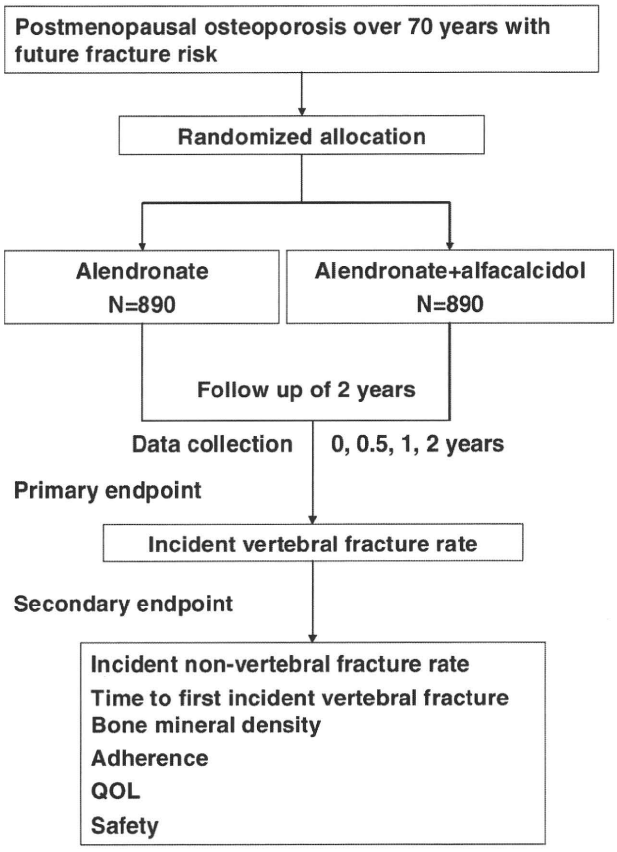

Fig. 1 Study design and outcomes

participants were selected by the practitioners and registered by Japan Clinical Research Support Unit (JCRSU), and then randomly allocated with a modified minimization method using age, number of pre-existing vertebral fracture number, bone mineral density (BMD) and value of bone metabolic marker into the group to be administered only ALN or the group that was to be administered both ALN and alfacalcidol. Registration and allocation of the participants were carried out on the Internet. After initiation of the assigned treatment, clinical data were collected at intervals of half a year for 2 years by I'cros Co., Ltd., through their visiting data collection service. Data were input to the database using a web system developed by ING Corporation. The primary endpoint was to compare the incident vertebral fracture rate between the intervention arms. The secondary endpoints were to compare the differences in the time to first incident vertebral fracture, non-vertebral fracture rate, bone mineral density, adherence, QOL and safety (Fig. 1). In addition, sub-group analyses categorized by baseline characteristics such as age, body mass index (BMI), serum 25-hydroxyl vitamin D levels, the number of pre-existing vertebral fractures and fracture grade were candidate factors. If participants wanted to change the designated treatment because of side effects or occurrence of fractures, they were permitted to do so, and follow-up observations were continued. Please see Table 1 and Fig. 1.

Sample size

Assumptions regarding the fracture rate in the ALN group were made based on a paper by Kushida et al. (Phase III trial for alendronate), in which it is reported that there was a 12.2% fracture rate during observations conducted over 2 years [8]. Since there are not much data on concurrent use of ALN and alfacalcidol [18], the authors' expectations were such that the effects of ALN would be added to those of alfacalcidol and that the hazard ratio of the alfacalcidol combined arm to ALN alone would be 0.64 [19]. The sample size was then estimated to be 890 cases per arm (two-sided alpha = 0.05, power = 0.8), taking account of a dropout rate of 10% referring to the value of the prior clinical trial of fracture intervention [4].

Fracture evaluation

X-ray films of conventional lateral radiographs of lumbar and thoracic vertebrae were taken and collected by I'cros Co., Ltd. After masking the patient's information, two

independent readers (orthopedist, TN and radiologist, MF) simultaneously reviewed films from T4 to L4 in chronological sequence and graded vertebral fracture based on a semi-quantitative method [20]. Before the start of the study, these two observers held meetings to make adjustments between their own criteria for grading vertebral fractures. When the diagnosis of pre-existing fractures made by the reviewers differed from those made by the practitioners, the reviewers' diagnosis was adopted preferentially. If inconsistencies arose between the readers in diagnosing pre-existing and incident vertebral fractures, the two readers negotiated between themselves to reach a consensus. Incident bone fractures other than those of the vertebrae were comprehended from the chart, and the occurrence of fractures was confirmed based on X-ray films or a record of the operation.

Clinical data

BMD at the lumbar vertebrae, hip (proximal femur), distal radius (dual energy X-ray absorptiometry) or left-sided second metacalpal bone (microdensitometry) was measured at baseline and at 6-month intervals for 2 years at each institute. The data of BMD obtained from the different machines and from different bone sites were calculated as the percentage change in each time point from the baseline value. The statistical difference in change of BMD between the group that received combined treatment and the group that was administered only ALN was compared based on each set of data for BMD for the different bone sites. Body height was measured at baseline, 12 and 24 months. Bone turnover markers (urinary type I collagen cross-linked N-telopeptide or urinary excretion of deoxypyridinoline) were measured at baseline and again 6 months after initiating treatment. QOL was assessed by using self-administered questionnaires (JOQOL and EQ-5D) at baseline and at 6, 12 and 24 months after initiating treatment [21]. Serum samples were sent to the central laboratory (SRL Co., Japan), and 25-hydroxyl vitamin D concentrations were measured. Other routine biochemical examinations were carried out at baseline and at 2 years after initiating treatment in order to estimate biochemical adverse events. All adverse events were reported to JCRSU, coded by MedDRA, and categorized as either "known" or "unknown." If an unknown adverse effect occurred, it was reported to the investigator and ethical committee.

Ethics and registration

Ethical issues regarding protocol were reviewed by the ethical committee for JOINT under the Declaration of Helsinki (Dr. Rikushi Morita, Chairman). If it turned out that a patient was at a disadvantage under observation, the ethical committee was given permission to stop the protocol. This study was registered at UMIN-CTR (University Hospital Medical Information Network—Clinical Trial Registry) with the number C000000001.

Statistical analysis

Analysis of the intent to treat principle was applied to the statistical analysis. Efficacy analysis uses a full analysis set (FAS), and all of the enrolled patients are applied to the analysis except for patients without efficacy data, patients who do not correspond to inclusion criteria and patients who do not receive treatment. The PPS (protocol per set) group is defined as consisting of patients without any serious protocol violation.

Recruitment of the practitioner

The explanatory meeting of the protocol and registration was held in all of Japan. The executive members of the A-TOP research group were responsible for the presentation of the protocol and for the recruitment of study institutions and practitioners. The A-TOP committee created the WEB site on the Internet so that the registration of the study could be executed directly. I'cros Co., Ltd., was also involved as a collaborator in calling practitioners.

Results and discussion

Several principles had to be considered for acceptance of concurrent treatment: firstly, the concurrent treatment should be clinically and statistically significantly more effective than the basic treatment; secondly, the concurrent treatment should be of the same level of safety as single treatment; thirdly, the concurrent treatment should be cost-effective. Although these principles should be evaluated before adopting concurrent treatment, the authors have applied concurrent treatment to osteoporosis widely, without any background evidence. Among these principles, the authors have decided to evaluate the first two issues, effectiveness and safety, in the present study. Since this type of evaluation is absolutely required by a clinician, a researcher-initiative study was considered as being the most suitable type of evaluation. This was the reason why the authors decided to use a researcher-initiative clinical trial in determining the effectiveness of concurrent treatment for osteoporosis. The JOINT-02 protocol was the first randomized, controlled trial conducted nationwide for osteoporosis in Japan initiated by researchers, and its scale was also the largest ever. It was therefore necessary for various organizations to collaborate together, and there

have been no previous reports on how to manage the PROBE trial in Japan. This is why we wanted to report the design of JOINT-02. In this paper, we have presented the organization of the A-TOP research group and execution of the JOINT 02 protocol. This is because we believe that this report should help a researcher who is willing to build a new nationwide investigation that is constructed by an organization of clinical research work.

Since the primary aim of JOINT-02 was to determine whether concurrent treatment using ALN and alfacalcidol is superior to treatment using ALN alone in terms of fracture prevention, true ("hard") endpoints such as vertebral fractures or long bone fractures were selected as the primary endpoint. The diagnosis of whether vertebral fractures were present or not on the X-ray films was made by two independent reviewers who did not have any information about the patient; when the judgment of fractures was split between the two reviewers, the reviewers negotiated with each other. Identifying vertebral fractures is more difficult than identifying long bone fractures due to some cases of new vertebral fractures not showing clinical symptoms and the shape of the vertebral body making it difficult at times to recognize whether there is a fracture. Therefore, to avoid misdiagnosis, diagnosis of pre-existing and incident vertebral fractures was made by two different observers. In cases where there was a discrepancy in the diagnosis of vertebral fractures between the reviewers and the practitioner, which occurred with regard to pre-existing fractures, the reviewers' judgment was given priority over that of the practitioner.

Surrogate ("soft") endpoints such as change in BMD or bone turnover markers were considered to be inadequate as primary endpoints in making conclusive statements regarding the efficacy of concurrent treatment. In this type of study, the soft endpoint (BMD or biomarkers) will connect dropout bias less effectively than the case-selected hard endpoint, because such markers are not able to be made blind to the clinicians. Furthermore, previous studies indicate that changes in BMD or bone markers do not predict future fractures [22–24].

In recent literature, it has been reported that poor adherence of bisphosphonates leads to a decline in the beneficial effects of this drug on bone [25–28]. It is expected that in contrast to prior developmental trials, this current study may have a higher dropout rate, since in a researcher-initiative study, the registered practitioner is not forced to maintain adherence very strictly. As a result, adherence in the present study may resemble the actual circumstances of adherence to bisphosphonate treatment by a general practitioner. It will be interesting to determine whether adherence in this study modifies fracture prevention by alendronate.

Although a careful plan for this study has been set up, the results will be applied to osteoporosis patients with the same background as the present study population, but not adapted to the entire osteoporosis population. Despite this limitation, we believe that the results will give us very important information regarding the concurrent treatment of osteoporosis.

Acknowledgments The authors express thanks to the chairman (Dr. Rikushi Morita) and the members of the ethics committee: Ms. Mamiko Matsumura, Dr. Tetsuro Inoue, Dr. Isao Yoshimura, Dr. Mitsuyoshi Nakajima, Tooru Ebihara, R.Ph., Mr. Shinya Hattori and Mr. Kousaku Uchida. This JOINT study was sponsored by the Public Health Research Foundation. The authors would like to thank those who participated as clinical investigators in JOINT-02. The authors also thank the Japan Arteriosclerosis Prevention Fund, Teijin Pharma Limited, Asahi Kasei Corporation, Takeda Pharmaceutical Company Limited, GE Healthcare Japan, Toyo Medic Co., Ltd., Banyu Pharmaceutical Co., Ltd., and Dainippon Sumitomo Pharma Co., Ltd., for their generous donations.

References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785–795
2. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J (2000) Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 15:1384–1392
3. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348:1535–1541
4. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
5. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA 282:1344–1352
6. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Glüer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
7. Shiraki M, Kushida K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, Kaneda K, Minaguchi H, Inoue T, Morii H, Tomita A, Yamamoto K, Nagata Y, Nakashima M, Orimo H (1999) A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. The

Alendronate Phase III Osteoporosis Treatment Research Group. Osteoporos Int 10:183–192
8. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H (2002) The efficacy of alendronate in reducing the risk for vertebral fracture in Japanese patients with osteoporosis. Curr Ther Res 63:606–620
9. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H (2004) Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 22:462–468
10. Sckett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS (1996) Evidence based medicine; what it is and what it isn't. Br Med J 312:71–72
11. Japanese Osteoporosis Guideline 2006, Chief editor: Hajime Orimo, Life science Publish corp (article in Japanese)
12. Ministry of Health, Labour and Welfare. http://www.imcj.go.jp/rinri/main/02.htm (article in Japanese)
13. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB (2004) International Committee of Medical Journal Editors. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. JAMA 292:1363–1364
14. Shiraki M, Ohta H, Hosoi T, Kuroda T, Orimo H (2003) A-TOP study plane (3), survey of bisphosphonate. Osteoporosis Jpn 11:665–669 (article in Japanese)
15. Fujita T, Orimo H, Inoue T, Kaneda K, Sakurai M, Morita R, Morii H, Yamamoto K, Takaoka K (1993) Double-blind multicenter comparative study with alfacalcidol of etidronate disodium (EHDP) in involutional osteoporosis. Clin Eval 21:261–302
16. Fukunaga M, Nakamura T, Shiraki M, Kuroda T, Ohta H, Hosoi T, Orimo H (2004) Absolute height reduction and percent height ratio of the vertebral body in incident fracture in Japanese women. J Bone Miner Metab 22:104–110
17. Shiraki M, Kuroda T, Nakamura T, Fukunaga M, Hosoi T, Orimo H, Makino K, Adequate Treatment of Osteoporosis (A-TOP) Research Group (2006) The sample size required for intervention studies on fracture prevention can be decreased by using a bone resorption marker in the inclusion criteria: prospective study of a subset of the Nagano Cohort, on behalf of the Adequate Treatment of Osteoporosis (A-TOP) Research Group. J Bone Miner Metab 24:219–225
18. Frediani B (1998) Effects of combined treatment with calcitriol plus alendronate on bone mass and bone turnover in postmenopausal osteoporosis two year of continuous treatment. Clin Drug Invest 15:235–244
19. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C (2002) Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev 23:570–578
20. Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR (1996) Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res 11:984–996
21. JOQOL Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
22. Delmas PD, Seeman E (2004) Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 34:599–604
23. Earstell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD (2003) Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 18:1051–1056
24. Seibel MJ, Naganathan V, Barton I, Grauer A (2004) Relationship between pretreatment bone resorption and vertebral fracture incidence in postmenopausal osteoporotic women treated with risedronate. J Bone Miner Res 19:323–329
25. Yood RA, Emani S, Reed JI, Lewis BE, Charpentier M, Lydick E (2003) Compliance with pharmacologic therapy for osteoporosis. Osteoporos Int 14:965–968
26. Gallagher AM, Rietbrock S, Olson M, van Staa TP (2008) Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res 23:1569–1575
27. Kamatari M, Koto S, Ozawa N, Urao C, Suzuki Y, Akasaka E, Yanagimoto K, Sakota K (2007) Factors affecting long-term compliance of osteoporotic patients with bisphosphonate treatment and QOL assessment in actual practice: alendronate and risedronate. J Bone Miner Metab 25:302–309
28. Rabenda V, Hiligsmann M, Reginster JY (2009) Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. Expert Opin Pharmacother 10:2303–2315

Geriatrics Gerontology INTERNATIONAL 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2011; **11:** *3–7*

COMMISSION REPORT

Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: Commission report of the Japan Geriatrics Society

Masahiro Akishita,[1] Hiroyuki Arai,[2] Hidenori Arai,[3] Takashi Inamatsu,[4] Masafumi Kuzuya,[5] Yusuke Suzuki,[5] Shinji Teramoto,[6] Katsuyoshi Mizukami,[7] Shigeto Morimoto[8] and Kenji Toba;[9] Working Group on Guidelines for Medical Treatment and Its Safety in the Elderly

[1]Department of Geriatric Medicine, The University of Tokyo, Tokyo, [2]Department of Geriatric Medicine, Tohoku University, Sendai, [3]Department of Geriatric Medicine, Kyoto University, Kyoto, [4]Tokyo Metropolitan Geriatric Hospital, Tokyo, [5]Department of Geriatric Medicine, Nagoya University, Nagoya, [6]National Hospital Organization Tokyo Hospital, Tokyo, [7]Department of Psychiatry, Tsukuba University, Tsukuba, [8]Department of Geriatric Medicine, Kanazawa Medical University, Kanazawa, and [9]National Center for Geriatrics and Gerontology Hospital, Obu, Japan

Aim: The Japan Geriatrics Society (JGS) developed the guidelines for medical treatment and its safety in the elderly and the list of potentially inappropriate medication use, a Japanese version of the Beers list, in 2005. The JGS working group in collaboration with the Japan Broadcasting Corporation conducted the survey to geriatricians to investigate their experiences of adverse drug reactions (ADR) caused by potentially inappropriate medications.

Methods: In September 2008, the survey mails were sent to all the JGS certified geriatricians ($n = 1492$). The questionnaire consisted of 1 year of experiences of ADR of any type, past experiences of ADR by the use of antipsychotic benzamides, hypnotic benzodiazepines, digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and additional drugs, and their attitudes to reduce the dose/number of drugs for the prevention of ADR.

Results: A total of 425 geriatricians responded (response rate 29%). Seventy-two percent experienced ADR within 1 year. Past experiences of ADR were reported by 79% for antipsychotic benzamides, 86% for hypnotic benzodiazepines, 70% for digoxin and 37% for vitamin D_3. Free responses included frequent ADR by non-steroidal anti-inflammatory, antihypertensive, antiplatelet, anti-arrhythmic, antidiabetic and antidepressant drugs. Reduction of drugs for ADR prevention was attempted by 93%.

Accepted for publication 28 Apr 2010.

Correspondence: Dr Masahiro Akishita MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: akishita-tky@umin.ac.jp

doi: 10.1111/j.1447-0594.2010.00631.x

Conclusion: This survey showed that most geriatricians experience ADR and take preventive measures for ADR. The results can be used for education and the development of new guidelines. **Geriatr Gerontol Int 2011; 11: 3–7.**

Keywords: adverse drug reactions, Beers list, geriatrician, polypharmacy, side-effect.

Introduction

Adverse drug reactions (ADR) are more frequent and severe in the elderly than in young adults. A recent systematic review[1] of prospective observational studies reported that 10.7% of hospital admissions were associated with ADR in elderly patients, while 6.3% were so in young adults. Surveys performed in acute care hospitals in Japan also showed that inpatients aged 70 years or older were 1.5-fold more likely to develop ADR than those under 60 years of age,[2] and that the ADR incidence among elderly inpatients was 6–15%.[3] It has been reported from Western countries that ADR occur in more than 10% of outpatients or nursing home residents.[4]

Although many factors relate to the high ADR incidence in the elderly, overdoses resulting from age-related changes of pharmacokinetics/pharmacodynamics and polypharmacy may be of critical importance.[2–4] Because the evidence for the elderly is limited, practical guidelines to medical treatment and its safety are required in the field of geriatric medicine.

The Japan Geriatrics Society (JGS) has conducted educational activities through scientific sessions and official journals to reduce ADR. As part of activities, the ad hoc committee "Working group on guidelines for medical treatment and its safety in the elderly" was set up in 2003, and the JGS guidelines for medical treatment and its safety in the elderly were published in 2005.[5] In the guidelines, the list of medications that should be prescribed with special attention to elderly patients was reported and was put on the JGS website. This list, a Japanese version of the Beers list,[6,7] consists of 45 drugs or drug classes that may be harmful or less efficient, thus potentially inappropriate for elderly patients, and can be applied to reduce ADR and polypharmacy in clinical settings of geriatric medicine and nursing-care facilities.[5]

Although the mass media expressed an interest in these activities, the JGS should increasingly accumulate the evidence and make a proposal on pharmacotherapy of the elderly for public education. For this purpose, the JGS working group in collaboration with the Japan Broadcasting Corporation (NHK) conducted the survey to JGS certified geriatricians to investigate their experiences of ADR caused by potentially inappropriate medications. This commission report of the working group shows the survey results.

Methods

Mailing and collection of the questionnaire

In September 2008, the questionnaire was mailed by the NHK to all the JGS certified geriatricians (n = 1492) who appeared on the JGS website. In the cover letter, a brief introduction including the background and aim of the survey was described, followed by the statement that this survey was carried out in collaboration with the NHK and the JGS working group. The JGS version of the Beers list (Table 1 and detailed explanation) was included in the mail for options of additional drugs. The responder was asked to return the questionnaire to the NHK by fax without his/her name.

Questionnaire item

The questionnaire consisted of 1-year experiences of ADR of any type (yes/no question), past experiences (frequent, occasional or none) of ADR by the use of antipsychotic benzamides (sulpiride, sultopride), hypnotic benzodiazepines (flurazepam, haloxazolam, quazepam, triaxolam), digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and free additions, and their attitudes to reduce the dose/number of drugs for the prevention of ADR (yes/no question). In addition, free comments on the problems and approaches related to pharmacotherapy in the elderly were asked. The above four classes of drugs were chosen from the JGS version of the Beers list (Table 1) because these drugs were considered frequently prescribed to elderly patients.

Statistical analysis

The data are shown as the number and the percent of subjects. The χ^2-test was performed to analyze the associations between ADR experiences.

Results

A total of 425 geriatricians responded, resulting in a response rate of 28.5%. The response rate would have been 29.1% if the 30 subjects to whom the mails were not successfully delivered were excluded.

The summary of the results is shown in Table 2. Seventy percent of the geriatricians reported

Table 1 List of medications that should be prescribed with special attention to elderly patients (JGS version of the Beers list)

Class	Drug (generic name)
Antihypertensive (central sympathetic blocking agents)	Methyldopa
	Clonidine
Antihypertensive (rauwolfia)	Reserpine
Antihypertensive (short-acting calcium channel blockers)	Nifedipine
Vasodilator	Isoxsuprine
Cardiac glycoside	Digoxin (≥0.15 mg/day)
Anti-arrhythmic	Disopyramide
	Amiodarone
Antiplatelet	Ticlopidine
Hypnotic (barbiturates)	Pentobarbital
	Amobarbital
	Barbital
	Chlorpromazine, promethazine, phenobarbital
Hypnotic (benzodiazepines)	Flurazepam
	Haloxazolam
	Quazepam
	Triaxolam
Anxiolytic (benzodiazepines)	Chlordiazepoxide, diazepam
Antidepressants	Tricyclic (amitriptyline, imipramine, clomipramine)
	Maprotiline
Antipsychotic (phenothiazines)	Thioridazine, chlorpromazine, levomepromazine
Antipsychotic (butyrophenones)	Haloperidol, timiperone, bromperidol
Antipsychotic (benzamides)	Sulpride, sultopride
Anti-parkinsonian	Trihexyphenidyl
Antiepileptic	Phenobarbital
	Phenytoin
Narcotic analgesic	Pentazocine
Non-steroidal anti-inflammatory	Indometacin
	Diclofenac sodium, naproxen, piroxicam
Irritant laxative	Caster oil
Skeletal muscle relaxant	Methocarbamol
Soothing muscle relaxant	Oxybutynin
Intestinal antispasmodic	Butylscopolamine
	Propantheline
Anti-emetic	Metoclopramide
	Domperidone
Androgen	Methyltestosterone
Estrogen	Estrogens
Thyroid hormone	Dried thyroid
Hypoglycemics (1st-generation sulfonyl urea)	Chlorpropamide
	Acetohexamide
Hypoglycemics (biguanides)	Metformin
	Buformine
Iron	Fe (≥300 mg/day)
Vitamin D	Alfacalcidol (≥1.0 μg/day)

Doses in the parentheses are applicable for digoxin, Fe and alfacalcidol. This list with detailed explanation such as trade names and alternative drugs was enclosed in the questionnaire.

experiences of ADR within a year, even though non-responders ($n = 7$) were included in those without experience. Regarding past experiences of ADR, approximately a quarter of the geriatricians reported frequent ADR experiences by antipsychotic benzamides and hypnotic benzodiazepines. Seventy to eighty percent frequently or occasionally experienced ADR by these two classes of drugs and by digoxin, and

Table 2 Geriatricians' experiences of adverse drug reactions (ADR) and their attitudes to reduce drugs for the prevention of ADR ($n = 425$)

1. One-year experiences of ADR of any type ($n = 418$)			71.5%
2. Past experiences of ADR by use of the following drugs			
	Frequent	Occasional	Frequent + Occasional
(i) Antipsychotic benzamides ($n = 381$) (sulpiride, sultopride)	93 (24.4%)	207 (54.3%)	300 (78.7%)
(ii) Hypnotic benzodiazepines ($n = 386$) (flurazepam, haloxazolam, quazepam, triaxolam)	93 (24.1%)	241 (62.4%)	334 (86.5%)
(iii) Digoxin (≥0.15 mg/day) ($n = 382$)	33 8.6%)	234 61.3%)	267 69.9%)
(iv) Vitamin D_3 ($n = 373$) (alfacalcidol ≥1.0 μg/day)	14 (3.7%)	125 (33.5%)	139 (37.3%)
3. Past experiences of ADR (free responses; $n = 240$)			
Class of drugs	Frequent	Occasional	Frequent + Occasional
(i) Non-steroidal anti-inflammatory	60	34	94
(ii) Antihypertensive	19	27	46
(iii) Antiplatelet	17	21	38
(iv) Antidiabetic	19	15	34
(v) Anti-arrhythmic	13	17	30
(vi) Antidepressant	15	10	25
(vii) Anti-Parkinson	9	12	21
(viii) Warfarin	6	7	13
4. Reduction of the dose/number of drugs for the prevention of ADR ($n = 417$)			93.0%

Data in the parentheses indicate the number of responses to each questionnaire item. Each value indicates the number of cases and the percentage. Free responses to past experiences of ADR show the classes of drugs with more than 10 cases.

nearly 40% by vitamin D_3. Interestingly, the χ-square test showed that 1-year experiences of ADR of any type were significantly associated with ADR experiences by each of the four classes of drugs (data not shown), suggesting that some geriatricians frequently experience ADR of various types, and others do not. Free responses ($n = 240$) included common ADR by non-steroidal anti-inflammatory drugs; 25% of the responders reported frequent ADR and 39% reported frequent or occasional ADR. More than 90% of the geriatricians reported that they reduced the dose and number of drugs for the prevention of ADR.

Free comments on the problems and approaches related to pharmacotherapy in the elderly were summarized as follows: (i) lack of understanding about drug metabolism and ADR by doctors and patients, and need for their education; (ii) training of geriatricians who understand medical treatment in the elderly and are able to align prescriptions in a comprehensive manner; (iii) medication errors and a lack of prescription information derived from multi-consultations are problematic, thus a medication management and interdisciplinary collaboration system must be established; and (iv) because a medical fee system in which an easy medication is profitable rather than attentive listening may cause polypharmacy, guidelines and a new medical system to block this pathway should be created.

Discussion

In this questionnaire survey, although the mails were sent from the NHK, approximately 30% of the JGS certified geriatricians responded, expressing their high interest in medical treatment in the elderly. Seventy percent of them reported ADR experiences within a year, while more than 90% attempted to reduce the dose and number of drugs for the prevention of ADR.

Although most geriatricians reported ADR experiences, the prevalence should be carefully interpreted. First, sampling bias and overestimation are possible, because geriatricians who experienced more ADR and were conscious of ADR might have responded more actively. Second, there is a problem in reliability of ADR, because judgments of ADR including causality and severity may vary between geriatricians, and ADR experiences were dependent on memory rather than records. The questionnaire item concerning the frequency of ADR for individual drugs was also ambiguous. Because the frequency of ADR is related to the frequency of prescriptions, free responses included many common medications for elderly patients, such as non-steroidal anti-inflammatory drugs and antihypertensive drugs.

As described above, this survey was not designed to determine the incidence of ADR per patient or drug. The aim was to accumulate the opinions of JGS certified

geriatricians about ADR and pharmacotherapy, thus the results may have reflected their awareness of the issues. Taken together, it is reasonable that antipsychotic benzamides, hypnotic benzodiazepines and digoxin (≥0.15 mg/day) are included in the JGS version of the Beers list, because 70–80% of geriatricians reported ADR experiences by these drugs. This questionnaire also asked about ADR by vitamin D, which was not included in the lists of potentially inappropriate medications in Western countries.[6–8] Vitamin D_3 (alfacalcidol ≥1.0 μg/day) was included in the JGS list, because this class of drugs are frequently and carelessly used at high doses with calcium preparations for treatment of osteoporosis, leading to hypercalcemia. The result that 37% experienced vitamin D-related ADR justified the inclusion of vitamin D in the list. Regarding additional classes of drugs with more than 10 responses, some drugs of all classes but warfarin were also included in the JGS list. Each drug with many responses should be considered for inclusion when the list is updated.

It is not surprising but important that 93% of geriatricians reduced drugs for the prevention of ADR. This may be a result of educational activities by the JGS and may represent advanced performance of JGS certified geriatricians. Educational efforts and public information to reduce ADR should be strengthened.

The data are not available about what percentage of patients received interventions for drug reduction. We reanalyzed the data of the ADR survey conducted in five university hospitals,[3] and found that the number of drugs were decreased in 20% of inpatients ($n = 1002$) during hospital stay, although the reason for drug reduction is unknown. The investigation of five long-term care facilities[9] showed that one or more drugs were discontinued after admission in 40% of 581 patients on medications. It is noteworthy that the numbers of drugs included in the 1997 version of the Beers list[6] were decreased by 33% (from 61 to 41 cases) in this investigation, even though these drugs were not selectively discontinued. In the future, prospective studies to survey the frequency of drug reduction per patient for ADR prevention, and interventional studies, preferably randomized controlled trials, to investigate the efficacy of drug review/reduction using the JGS version of the Beers list needs to be performed.

Finally, free comments should be appreciated. Various problems and proposals raised from clinical practice are reasonable and were summarized as described in the results section. Other comments included the issue of drug dependency or fear of some patients, effectiveness-biased advertisements by pharmaceutical companies and disease-specific guidelines neglecting the individual difference, leading to the high ADR incidence and inappropriate medication management in elderly patients. Based on the results and comments obtained from this survey, the JGS and geriatricians should promote researches and accumulate the evidence concerning pharmacotherapy in the elderly to develop new guidelines and advance educational activities.

Acknowledgments

We thank the staff of the NHK TV program "Close-up Gendai", especially Mr Mamoru Ichikawa and Mr Tatsuo Yonehara for their full cooperation to complete this survey, and the 425 geriatricians who responded to this questionnaire.

References

1 Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 2008; **42**: 1017–1025.
2 Toba K, Akishita M, Mizuno Y *et al.* Adverse drug reaction in the elderly. *Jpn J Geriatr* 1999; **36**: 181–185.
3 Arai H, Akishita M, Teramoto S *et al.* Incidence of adverse drug reactions in geriatric units of university hospitals. *Geriatr Gerontol Int* 2005; **5**: 293–297.
4 Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; **160**: 2717–2728.
5 The Japan Geriatrics Society. *Guidelines for Medical Treatment and Its Safety in the Elderly 2005*. Tokyo: Medical View, 2005 (in Japanese).
6 Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531–1536.
7 Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; **163**: 2716–2724.
8 McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997; **156**: 385–391.
9 Mita Y, Akishita M, Tanaka K *et al.* Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. *Geriatr Gerontol Int* 2004; **4**: 146–150.

Hypertension Research (2011) 34, 474–478

www.nature.com/hr

ORIGINAL ARTICLE

Association between human metapneumovirus seroprevalence and hypertension in elderly subjects in a long-term care facility

Li Zeng, Rui Chen, Keiichiro Ishigami, Mikiko Atsumi, Yumi Koizumi, Kazuto Sato, Osamu Iritani, Masashi Okuro and Shigeto Morimoto

Recently, relations between hypertension and infections caused by several pathogens have been reported. However, few studies have examined the relationship between human metapneumovirus (hMPV) and hypertension in elderly inpatients. To assess the association between anti-hMPV-immunoglobulin G (IgG) titer and the prevalence of hypertension, we conducted a case–control study in a Japanese long-term care facility (LTCF). The participants included 84 hypertensive patients aged ⩾65 years, and 84 age- and sex-matched normotensive controls (38 males and 46 females in each group; cases, 79.9 ± 8.4 (s.d.) years; controls, 80.1 ± 8.3 years). Data on underling chronic clinical conditions were collected. Titers were measured using an immunofluorescence assay kit. The significance of risk factor differences was analyzed using univariate and multivariate comparisons of cases and controls. All serum samples were positive for hMPV, and IgG titers ranged from 40-fold to more than 5120-fold. There were no significant sex- or age-related differences in $\log_2$ (anti-hMPV-IgG titer/10) among the subjects. Compared with normotensive subjects, hypertensive patients presented significantly higher $\log_2$ (anti-hMPV-IgG titer/10) values ($P<0.001$). After adjustment with multiple logistic analysis, the odds ratio for $\log_2$ (anti-hMPV-IgG titer/10) was 1.42 (95% confidence interval 1.16–1.75, $P=0.001$) relative to normotensive subjects. In all subjects, stepwise multiple regression analysis revealed that both hypertension and a poor nutritional state independently contributed to increased $\log_2$ (anti-hMPV-IgG titer/10). These observations suggest that an increased anti-hMPV-IgG titer was closely related to hypertension in elderly subjects in a Japanese LTCF.
Hypertension Research (2011) **34**, 474–478; doi:10.1038/hr.2010.268; published online 20 January 2011

Keywords: elderly; human metapneumovirus; seroprevalence

INTRODUCTION

Human metapneumovirus (hMPV) was first isolated in children with acute respiratory tract illnesses in 2001.[1] This virus is a member of the genus metapneumovirus of the subfamily Pneumovirinae of the family Paramyxoviridae. hMPV induces infections of the lower respiratory tract, including bronchitis, bronchiolitis and pneumonia, in young children[2] and immunocompromised individuals,[3] along with upper respiratory tract illnesses and influenza-like illness.[4] In January 2005, we reported an outbreak of nosocomial hMPV infection in elderly subjects in a long-term care facility (LTCF) in Japan.[5] Several subsequent reports revealed that hMPV infection outbreaks frequently occur in LTCFs,[6] not only in the winter[5,6] but also in summer,[7] with high mortality. Serological responses to hMPV-induced respiratory tract illnesses were frequently found (12.8%) among common viruses during a 52-week intervention period in residents of an LTCF.[8] Unlike other viral infections, which evoke lifelong immunity, hMPV reinfection occurs frequently, despite high rates of perpetual seroprevalence for all age groups. This finding suggests that reinfection occurs because humoral immune responses have a minor role in the clearance of hMPV.[9] However, the relationship between hMPV infection and the underlying chronic clinical conditions has not been adequately evaluated in elderly subjects. Therefore, the aim of this study was to determine the relationship between the titer of immunoglobulin (Ig) G antibody against hMPV (anti-hMPV-IgG titer) and clinical conditions, including hypertension, in elderly patients in a Japanese LTCF.

METHODS

Identification of cases and controls

Our study was conducted in a 640-bed ward of the Department of Internal Medicine of Hanwa-Senboku Hospital, a Japanese LTCF for the elderly. The research protocol was approved by the ethics committee of the hospital. We identified all elderly subjects aged ⩾65 years with hypertension, which was defined as blood pressure of >140/90 mm Hg or antihypertensive medication use. The controls were a random sample of normotensive subjects aged ⩾65 years admitted to the same ward. The computerized admission lists served as the sampling frame, and we frequency matched the controls to the cases by sex

Department of Geriatric Medicine, Kanazawa Medical University, Ishikawa, Japan
Correspondence: Professor S Morimoto, Department of Geriatric Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan.
E-mail: shigeto@kanazawa-med.ac.jp
Received 11 September 2010; revised 8 October 2010; accepted 9 October 2010; published online 20 January 2011

and age (±2 years) at a ratio of 1:1. The controls met the same eligibility criteria as the cases, but they did not have hypertension. All subjects who gave informed consent were enrolled in our study, and the blood samples were obtained between October and November 2007. Subjects were excluded if they (1) had a clinical diagnosis of secondary hypertension due to other diseases at the beginning of the study, (2) had serum creatinine levels $\geqslant 177\,\mu mol\,l^{-1}$ ($2.0\,mg\,dl^{-1}$), (3) were in the critical phase of another acute illness (myocardial infarction, stroke, exacerbation of heart failure, pneumonia or renal failure), (4) received artificial feeding or (5) were immunocompromised because of systemic steroid use, metastatic cancer or cancer therapy.

Measurement of IgG titer against hMPV

IgG titer was measured using an indirect immunofluorescence assay kit from Mitsubishi Kagaku Bio-Clinical Laboratories (Tokyo, Japan), as described previously.[10] Serum that reacted with F protein at a dilution of ⩾1:10 was defined as positive for anti-hMPV antibodies. IgG titers were calculated according to $\log_2$ (anti-hMPV-IgG titer/10) for each serum sample, and the positive results at dilutions of 1:10 to 1:5120 were rated on a scale from 0 to 9.

Underlying chronic conditions

In Table 1, we noted the presence of the following clinical features in the enrolled patients: stroke, ischemic heart disease, chronic congestive heart failure, chronic kidney disease,[11,12] dementia,[13] diabetes mellitus, dyslipidemia,[14] a bedridden state, obesity,[14] a poor nutritional state and lung disease. The personal physicians of the patients were involved in the diagnosis of these complications, which were further assessed by a committee consisting of the authors (except MO). Objective and routinely collected medical information was used to enhance the accuracy of the diagnoses. Only chronic conditions were recorded for the cases and their respective control subjects. A computerized pharmacy database was used to assess the drug use. Each pharmacy record included the drug type and dose, date and administration duration. Data collection for the controls commenced after they had been hospitalized the same number of weeks as their corresponding cases. The data were retrieved from medical records (by MO). Of the 84 elderly subjects with hypertension, 21 took angiotensin II-receptor blockers alone, 16 took angiotensin I-converting enzyme inhibitors alone, 18 took dihydropyridine calcium-channel blockers alone and 10 took two or more (out of three) classes of antihypertensives, plus diuretics. In all, 19 subjects with hypertension were not prescribed any antihypertensive agent.

Statistical analysis

Data are expressed as mean and s.d. for continuous variables. Between-group comparisons were conducted with a Mann–Whitney *U*-test or χ^2-test (Fisher's exact test when needed). Independently participating factors for hypertension were identified by multiple logistic regression analysis after adjustment for confounding variables. Common pitfalls associated with multivariate regression were avoided using the method described by Concato *et al.*[15] The odds ratio (OR) for hypertension associated with various conditions was calculated using logistic regression analysis, adjusting for age, sex, and all associated variables selected according to their univariate analysis *P*-value ($P<0.20$).[16] Estimates for OR and the corresponding two-sided 95% confidence intervals (CIs) that demonstrated statistical significance were derived from the regression model. Conditional logistic regression was used to control for potential confounding variables. Independent associations with $\log_2$ (anti-hMPV IgG titer/10) titer values were assessed by stepwise multiple regression analysis, using age, sex and factors with *P*-values <0.2 in the univariate analysis. *P*-values <0.05 were considered significant. The data were analyzed using SPSS (v. 16.0, Chicago, IL, USA).

RESULTS

Confirmation of clinical factors

Table 2 summarizes the clinical background and underlying chronic conditions in the control and hypertension groups. There were no significant differences between the two groups in age, sex, admission period or prevalence of diabetes mellitus, dyslipidemia, or underlying chronic conditions, except that the hypertension group tended toward a higher prevalence of a past history of stroke and chronic kidney disease than the control group.

Anti-hMPV-IgG titer in normotensive and hypertensive elderly inpatients

All serum samples were positive for anti-hMPV-IgG. The titer ranged from 40× to more than 5120× in the 168 elderly inpatients, and the mean ± s.d. value of $\log_2$ (anti-hMPV-IgG titer/10) was 6.19 ± 1.65. The mean ± s.d. value of $\log_2$ (anti-hMPV-IgG titer/10) in the hypertension group (6.63 ± 1.52) was significantly higher than in the control group (5.75 ± 1.67; $P=0.001$; Figure 1). There was no significant difference in the mean ± s.d. $\log_2$ (anti-hMPV-IgG titer/10) values between any two subgroups with antihypertensive treatment in the hypertensive elderly subjects: 6.69 ± 1.49 in the angiotensin II-receptor blocker group ($n=21$, $P=0.038$); 6.57 ± 1.66 in the angiotensin I-converting enzyme inhibitor group ($n=16$, $P=0.041$); 6.50 ± 1.46 in the calcium-channel blocker group ($n=18$); 6.30 ± 1.64 in multi-antihypertensive group ($n=10$); and 6.95 ± 1.47 in the non-treatment

Table 1 Operational definitions for each pre-existing chronic condition were established prior to data collection

Clinical feature	*Definition*
Stroke	Motor deficit and evidence of stroke on CT and/or MRI
Ischemic heart disease	Evidence on ECG and echocardiography
Chronic congestive heart failure	LVEF ⩽40%
Chronic kidney disease	Estimated GFR calculated by the MDRD equation[11] with coefficients modified for Japanese patients,[12] $194\times Cr^{-1.094}\times age^{-0.287}$ (×0.739 if female) $<60\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$
Diabetes mellitus	Overnight FPG ⩾7.0 mmol l^{-1} (126 mg dl^{-1}) or the use of hypoglycemic agents and/or insulin
Dementia	MMSE ⩽23 (Folstein *et al.*[13])
Dyslipidemia	Overnight fasting plasma TC value ⩾5.72 mmol l^{-1} (220 mg dl^{-1}), TG ⩾1.70 mmol l^{-1} (150 mg dl^{-1}), HDL-C <1.04 mmol l^{-1} (40 mg dl^{-1}), or use of lipid-lowering agent[14]
Bedridden state	Permanently confined to bed
Obesity	BMI ⩾25 (Bando *et al.*[14])
Hypoalbuminemia	ALB level <30 g l^{-1}
Lung disease	Chronic bronchitis, pulmonary emphysema, severe bronchiectasis, chronic ILD, or sequelae of TB

Abbreviations: ALB, serum albumin; BMI, body mass index; CT, computed tomography; ECG, electrocardiography; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MMSE, mini-mental state examination score; MRI, magnetic resonance imaging; TB, tuberculosis; TC, total cholesterol; TG, triglycerides.

Table 2 Clinical factors in hypertensive patients (n=84) and normotensive controls (84)

	Normotensives (n=84)	*Hypertensives (n=84)*
Clinical background		
Age (years)	80.1±8.3	79.9±8.4
Male/female	38/46	38/46
Admission period (weeks)	131±56	132±55
Systolic blood pressure (mm Hg)	119±13	150±28***
Diastolic blood pressure (mm Hg)	69±10	86±17***
Anti-hMPV-IgG titer		
Log_2 (anti-hMPV-IgG titer/10)	5.75±1.67	6.63±1.52***
Underlying chronic conditions		
Stroke	36 (42.9%)	45 (53.6%)†
Ischemic heart disease	14 (16.7%)	20 (23.8%)
Chronic congestive heart failure	9 (10.7%)	6 (7.1%)
Chronic kidney disease	14 (16.7%)	21 (25.0%)†
Dementia	48 (57.1%)	46 (54.8%)
Diabetes mellitus	4 (4.8%)	9 (10.7%)
Dyslipidemia	30 (35.7%)	32 (38.1%)
Bedridden state	12 (14.3%)	14 (16.0%)
Obesity	17 (20.2%)	25 (29.8%)
Poor nutritional state	13 (15.5%)	11 (13.1%)
Lung disease	13 (15.5%)	16 (19.0%)

Abbreviations: hMPV, human metapneumovirus; IgG, immunoglobulin G.
Values are mean (±s.d.) or n (%).
***P<0.001, †P<0.20; case–control difference, by χ^2-test.

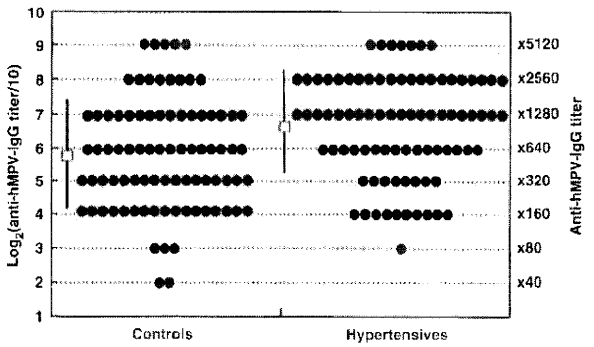

Figure 1 Anti-hMPV-IgG titer shown as log_2 (anti-hMPV-IgG titer/10) values in elderly inpatients in the control and hypertension groups. Circles indicate individual anti-hMPV IgG titers in elderly subjects. Open squares indicate means, and bars±s.d. values, in the control and hypertension groups, respectively.

group (n=19). The mean values of log_2 (anti-hMPV-IgG titer/10) in the angiotensin II-receptor blocker (P=0.075), angiotensin I-converting enzyme inhibitor (P=0.339) and non-treatment groups were significantly higher (P=0.005) than in the normotensive elderly subjects.

Multiple logistic regression analysis for independent association with hypertension

Multivariate associations between hypertension risk and selected characteristics after adjustment for potential confounders are shown in Table 3. Age, sex, log_2 (anti-hMPV-IgG titer/10) value, chronic kidney disease and stroke history were used as potential confounders. The log_2 (anti-hMPV-IgG titer/10) value was significantly related to an increased hypertension risk after adjustment for age, sex and potential confounding factors, with a matched OR estimate for hypertension of 1.42 (95% CI, 1.16–1.75, P=0.001; Table 3). Conditional logistic regression analysis using the same confounding factors revealed that log_2 (anti-hMPV-IgG titer/10) was significantly related to an increased hypertension risk, both in the hypertension subjects treated with any of the antihypertensive agents (n=65, OR: 1.34, 95% CI: 1.07–1.67, P=0.011) and in untreated hypertensive subjects (n=19, OR: 1.60, 95% CI: 1.10–2.31, P=0.013).

Table 3 Multivariate association between selected characteristics and odds ratio of hypertension

Characteristic (unit)	*Wald*	*Odds ratio*	*95% Confidence interval*	P
Log_2 (anti-hMPV-IgG titer/10)	8.64	1.42	1.16–1.75	0.001
Chronic kidney disease	2.40	1.91	0.86–4.33	0.122
Stroke	2.32	1.67	0.86–3.25	0.128
Age (years)	0.29	0.99	0.95–1.03	0.588
Male sex	0.00	1.01	0.52–1.95	0.972

Abbreviations: hMPV, human metapneumovirus; IgG, immunoglobulin G.
Analyzed by multiple logistic regression analysis.

Table 4 Log_2 (anti-hMPV-IgG titer/10) in subjects with and without clinical conditions

	Absence (n)	*Presence (n)*
Clinical background		
Age>80 years	6.12±1.58 (83)	6.26±1.73 (85)
Male	6.09±1.74 (92)	6.32±1.54 (76)
Underlying chronic conditions		
Stroke	6.19±1.64 (81)	6.20±1.68 (87)
Ischemic heart disease	6.20±1.68 (134)	6.15±1.59 (34)
Chronic congestive heart failure	6.20±1.65 (153)	6.07±1.71 (15)
Chronic kidney disease	6.17±1.63 (133)	6.29±1.74 (35)
Dementia	6.01±1.63 (74)	6.33±1.67 (94)
Diabetes mellitus	6.23±1.66 (155)	5.69±1.55 (13)
Dyslipidemia	6.12±1.63 (106)	6.31±1.69 (62)
Bedridden state	6.17±1.66 (142)	6.31±1.62 (26)
Obesity	6.08±1.70 (126)	6.52±1.49 (42)†
Poor nutritional state	6.09±1.68 (144)	6.79±1.38 (24)*
Lung disease	6.14±1.65 (139)	6.34±1.70 (29)

Abbreviations: hMPV, human metapneumovirus; IgG, immunoglobulin G.
†P<0.20, *P<0.05; case–control difference, by Mann–Whitney analysis.

Relationship between log_2 (anti-hMPV-IgG titer/10) and chronic clinical conditions

Table 4 compares log_2 (anti-hMPV-IgG titer/10) values between the groups with and without chronic clinical conditions, including older age (>80 years), male sex, obesity (body mass index $\geq 25\,kg\,m^{-2}$), diabetes mellitus, dyslipidemia, stroke, ischemic heart disease, chronic congestive heart failure, chronic kidney disease, dementia, a bedridden state, a poor nutritional state represented by hypoalbuminemia, and lung disease. The log_2 (anti-hMPV-IgG titer/10) value was significantly (P=0.020) higher in the 24 subjects with a poor nutritional state than in the 144 subjects with good nutrition. The log_2

Table 5 Stepwise multiple regression analysis to assess independent determinants for log_2 (anti-hMPV-IgG titer/10)

Characteristic (unit)	*β*	*t*	P
Hypertension	0.261	3.610	<0.001
Poor nutritional state	1.89	2.51	0.013
Obesity	0.086	1.150	0.256
Male sex	0.067	0.906	0.369
Age (years)	0.036	0.481	0.622

Abbreviations: hMPV, human metapneumovirus; IgG, immunoglobulin G.

(anti-hMPV-IgG titer/10) value tended to be higher (P=0.190) in obese subjects (body mass index $\geqslant 25\,kg\,m^{-2}$) than in non-obese subjects. There was no significant difference between the groups with and without other clinical conditions (Table 4). To determine the associating factors for log_2 (anti-hMPV-IgG titer/10) in all elderly subjects, a multiple stepwise regression analysis was carried out using age, sex, hypertension, a poor nutritional state and obesity as confounding factors. The analysis revealed that a poor nutritional state and hypertension were independent contributing factors for increases in log_2 (anti-hMPV-IgG titer/10) values in all subjects (Table 5).

DISCUSSION

The present case–control study revealed that anti-hMPV-IgG titer was independently associated with hypertension after adjusting for confounding factors in elderly subjects in an LTCF. Moreover, the multiple stepwise regression analysis revealed that hypertension and a poor nutritional state, among many underlying clinical conditions, contributed to increases in serum anti-hMPV-IgG titer in all elderly subjects. Although subjects with a poor nutritional state, reflected by hypoalbuminemia, are known to be susceptible to viral infection,[17] the findings in this study that this condition was also a risk factor for hMPV infection in elderly subjects in LTCFs is novel.

The precise mechanism(s) underlying the role of hypertension in anti-hMPV-IgG titer increases is unclear. One possible explanation is that some antihypertensive agents influenced the hMPV infection. In this study, however, there were no significant anti-hMPV IgG titer differences between any two subgroups of antihypertensive treatment, including the non-treatment subgroup in hypertensive elderly subjects; furthermore, the mean log_2 (anti-hMPV-IgG titer/10) values in the angiotensin II-receptor blocker, angiotensin I-converting enzyme inhibitor and non-treatment subgroups were significantly higher than in the normotensive elderly subjects. These observations suggest that antihypertensive agents have a minimal role in the increased anti-hMPV-IgG titers observed in the hypertensive elderly group.

The second possibility is that hypertension itself may cause higher anti-hMPV-IgG titers in the elderly. It is reported that patients with hypertension have significantly higher serum IgG levels in comparison with normotensive controls,[18] and that serum IgG levels were increased in patients who survived malignant phase hypertension.[19] Meanwhile, there have been several reports regarding the seroprevalence of hMPV infection around the world. Almost all people acquire seropositivity for hMPV by the age of 10 years,[2] and hMPV is known to infect individuals repeatedly throughout adult life and into old age.[5–9] Although there are no reports of IgG titer differences between patients with hypertension and normotensive controls after individual infections with pathogens, including hMPV, it is possible that hypertension itself may increase the anti-IgG titer in response to repeated hMPV infections in the elderly. In this present cross-sectional study, however, we could not show any time-course data for anti-hMPV-IgG titers in individual subjects.

The third possibility is that hypertension is the result of repeated hMPV infection. Several reports have associated the appearance of hypertension with predisposing repeated and/or chronic infections with many other pathogens, including *Chlamydia pneumoniae*,[20] herpes simplex virus type 2,[21] cytomegalovirus,[22] Coxsackie virus,[23] and *Helicobacter pylori*.[24] All these pathogens are known to directly affect vascular smooth muscle cells and/or vascular endothelial cells and to possibly cause the progression of atherosclerosis.[20–29] On the contrary, there is no evidence to date that hMPV has a direct effect on vascular smooth muscle cells or endothelial cells. hMPV is reported to affect airway epithelial cells and stimulate massive production of interleukin-8,[30,31] and regulate upon activation normal T-cell expressed and secreted.[31] On the other hand, interleukin-8 is known to closely relate to the genesis of hypertension because it enhances membrane permeability to Ca^{2+} and induces vasoconstriction in smooth muscle cells[32] and because an antihypertensive calcium channel blocker, azelnidipine, is reported to reduce circulating interleukin-8 levels.[33] Moreover, circulating interleukin-8 is known to predict the development of atherosclerosis in coronary arteries.[34] On the other hand, regulate upon activation normal T-cell expressed and secreted is known to be a peripheral monocyte-related inflammatory marker related to hypertension.[35] It is possible that repeated hMPV infections cause spillover of these cytokines from the respiratory tract into the circulation, laying the foundation for hypertension in the elderly. Consequently, the findings of this study suggest that serum anti-hMPV-IgG titers contribute to the risk factors for hypertension in the elderly in LTCFs. Nevertheless, the specific underlying pathophysiological mechanisms that link hMPV with hypertension in the elderly have not yet been defined. Therefore, the precise mechanisms underlying the association between hMPV infection and hypertension should be determined in future basic and clinical studies.

ACKNOWLEDGEMENTS

This work was supported by the Research Funding for Longevity Sciences (20A-02) from the National Center for Geriatrics and Gerontology Japan, Comprehensive Research on Aging and Health, the Ministry of Health, Labour and Welfare, and grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

1 van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, Osterhaus AD. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; **7**: 719–724.
2 Ebihara T, Endo R, Kikuta H, Ishiguro N, Yoshioka M, Ma X, Kobayashi K. Seroprevalence of human metapneumovirus in Japan. *J Med Virol* 2003; **70**: 281–283.
3 Pelletier G, Déry P, Abed Y, Boivin G. Respiratory tract reinfections by the new human metapneumovirus in an immunocompromised child. *Emerg Infect Dis* 2002; **8**: 976–978.
4 Stockton J, Stephenson I, Fleming D, Zambon M. Human metapneumovirus as a cause of community-acquired respiratory illness. *Emerg Infect Dis* 2002; **8**: 897–901.
5 Honda H, Iwahashi J, Kashiwagi T, Imamura Y, Hamada N, Anraku T, Ueda S, Kanda T, Takahashi T, Morimoto S. Outbreak of human metapneumovirus infection in elderly inpatients in Japan. *J Am Geriatr Soc* 2006; **54**: 177–180.
6 Boivin G, De Serres G, Hamelin MF, Côté S, Argouin M, Tremblay G, Maranda-Aubut R, Sauvageau C, Ouakki M, Boulianne N, Couture C. An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. *Clin Infect Dis* 2007; **44**: 1152–1158.
7 Louie JK, Schnurr DP, Pan CY, Kiang D, Carter C, Tougaw S, Ventura J, Norman A, Belmusto V, Rosenberg J, Trochet G. A summer outbreak of human metapneumovirus infection in a long-term-care facility. *J Infect Dis* 2007; **196**: 705–708.
8 Falsey AR, Dallal GE, Formica MA, Andolina GG, Hamer DH, Leka LL, Meydani SN. Long-term care facilities: a cornucopia of viral pathogens. *J Am Geriatr Soc* 2008; **56**: 1281–1285.

9 Lüsebrink J, Wiese C, Thiel A, Tillmann RL, Dilt V, Müller A, Schildgen O, Schildgen V. High seroprevalence of neutralizing capacity against human metapneumovirus in all age groups studied in Bonn, Germany. *Clin Vaccine Immunol* 2010; **17**: 481–484.
10 Ishiguro N, Ebihara T, Endo R, Ma X, Shirotsuki R, Ochiai S, Ishiko H, Kikuta H. Immunofluorescence assay for detection of human metapneumovirus-specific antibodies by use of baculovirus-expressed fusion protein. *Clin Diagn Lab Immunol* 2005; **12**: 202–205.
11 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; **130**: 461–470.
12 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, on behalf of the collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
13 Folstein M, Folstein S, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
14 Bando Y, Kanehara H, Aoki K, Katoh K, Toya D, Tanaka N. Characteristics of undiagnosed diabetes mellitus in a population undergoing health screening in Japan: target populations for efficient screening. *Diabetes Res Clin Pract* 2009; **83**: 341–346.
15 Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, Wolozin B, Sano M, Cruz-Sanchez FF, Thal LJ, Petanceska SS, Refolo LM. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology* 2003; **61**: 199–205.
16 Sano R, Abe R, Oikawa S, Fujii Y, Hori S, Suzuki N, Toyota T, Goto Y. Apolipoprotein E phenotypes of normo- and hyperlipoproteinemia in Japanese. *Tohoku J Exp Med* 1988; **154**: 297–303.
17 Katona P, Katona Apte J. The interaction between nutrition and infection. *Clin Infect Dis* 2008; **46**: 1582–1588.
18 Khraibi AA. Association between disturbances in the immune system and hypertension. *Am J Hypertens* 1991; **4**: 635–641.
19 Martinez-Amenós A, Buendia E, Carreras L, Font I, Mestre M, Rama H, Sarrias X, Alsina J. Humoral and cellular immunological abnormalities in hypertensive patients. *J Clin Hypertens* 1985; **1**: 153–160.
20 Cook PJ, Lip GY, Davies P, Beevers DG, Wise R, Honeybourne D. Chlamydia pneumoniae antibodies in severe essential hypertension. *Hypertension* 1998; **31**: 589–594.
21 Sun Y, Pei W, Wu Y, Jing Z, Zhang J, Wang G. Herpes simplex virus type 2 infection is a risk factor for hypertension. *Hypertens Res* 2004; **27**: 541–544.
22 Blum A, Peleg A, Weinberg M. Anti-cytomegalovirus (CMV) IgG antibody titer in patients with risk factors to atherosclerosis. *Clin Exp Med* 2003; **3**: 157–160.
23 Liu L, Liu Y, Tong W, Ye H, Zhang X, Cao W, Zhang Y. Pathogen burden in essential hypertension. *Circ J* 2007; **71**: 1761–1764.
24 Barnes RJ, Uff JS, Dent JC, Gear MW, Wilkinson SP. Long-term follow-up of patients with gastritis associated with Helicobacter pylori infection. *Br J Gen Pract* 1991; **41**: 286–288.
25 Kol A, Bourcier T, Lichtman AH, Libby P. Chlamydial and human heat shock protein 60s activate human vascular endothelium, smooth muscle cells, and macrophages. *J Clin Invest* 1999; **103**: 571–577.
26 Espinola-Klein C, Rupprecht HJ, Blankenberg S, Bickel C, Kopp H, Victor A, Hafner G, Prellwitz W, Schlumberger W, Meyer J. Impact of infectious burden on progression of carotid atherosclerosis. *Stroke* 2002; **33**: 2581–2586.
27 Billstrom Schroeder M, Worthen GS. Viral regulation of RANTES expression during human cytomegalovirus infection of endothelial cells. *J Virol* 2001; **75**: 3383–3390.
28 Godeny EK, Sprague EA, Schwartz CJ, Gauntt CJ. Coxsackievirus group B replication in cultured fetal baboon aortic smooth muscle cells. *J Med Virol* 1986; **20**: 135–149.
29 Iriz E, Cirak MY, Engin ED, Zor MH, Erer D, Ozdogan ME, Turet S, Yener A. Detection of Helicobacter pylori DNA in aortic and left internal mammary artery biopsies. *Tex Heart Inst J* 2008; **35**: 130–135.
30 Jartti T, van den Hoogen B, Garofalo RP, Osterhaus AD, Ruuskanen O. Metapneumovirus and acute wheezing in children. *Lancet* 2002; **360**: 1393–1394.
31 Bao X, Liu T, Spetch L, Kolli D, Garofalo RP, Casola A. Airway epithelial cell response to human metapneumovirus infection. *Virology* 2007; **368**: 91–101.
32 Buemi M, Marino D, Floccari F, Ruello A, Nostro L, Aloisi C, Marino MT, Di Pasquale G, Corica F, Frisina N. Effect of interleukin 8 and ICAM-1 on calcium dependent outflow of K+ in erythrocytes from subjects with essential hypertension. *Curr Med Res Opin* 2004; **20**: 19–24.
33 Komoda H, Inoue T, Node K. Anti-inflammatory properties of azelnidipine, a dihydropyridine-based calcium channel blocker. *Clin Exp Hypertens* 2010; **32**: 121–128.
34 Boekholdt SM, Peters RJ, Hack CE, Day NE, Luben R, Bingham SA, Wareham NJ, Reitsma PH, Khaw KT. IL-8 plasma concentrations and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1503–1508.
35 Parissis JT, Korovesis S, Giazitzoglou E, Kalivas P, Katritsis D. Plasma profiles of peripheral monocyte-related inflammatory markers in patients with arterial hypertension. Correlations with plasma endothelin-1. *Int J Cardiol* 2002; **83**: 13–21.

J Kanazawa Med Univ 35 : 166−171, 2010

Increased Level of LDL Cholesterol in Elderly Patients with Acute Ischemic Stroke Associated with Severe Hypertension

Mikiko Atsumi, Yumi Koizumi, Keiichiro Ishigami, Kazuto Satoh,
Osamu Iritani, Masashi Okuro and Shigeto Morimoto

Abstract: Low-density lipoprotein (LDL)-cholesterol is an independent risk factor for cardiovascular disease (CVD). We hypothesized that patients with the acute-phase of ischemic stroke associated with severe hypertension (>200/120 mmHg) would demonstrate a higher LDL-cholesterol level than either those with moderate hypertension (160-199/100-119 mmHg) or normotensive or mildly hypertensive (<160/100 mmHg) controls. We compared 20 elderly patients with CVD complicated with severe hypertension to 87 patients with moderate hypertension as well as 55 control patients during the first 72 hours after symptom onset of stroke. Patients receiving a lipid-lowering agent were excluded from the study. Serum LDL-cholesterol level was significantly higher in the severe hypertension group, compared to either the moderately hypertension group or the control group. High-density lipoprotein (HDL)-cholesterol and triglyceride levels were similar in all three groups. Serum total-cholesterol and LDL-cholesterol level were significantly higher in the severe hypertension group compared to the control group after adjusting for confounding variables. Severe hypertension is associated with an abnormal lipid profile, characterized by high LDL-cholesterol level. This dyslipidemia may be partly responsible for the vascular complications and the poor prognosis of these patients.

Key Words: elderly, ischemic stroke, severe hypertension, dyslipidemia

INTRODUCTION

Acute hypertension is frequently observed in patients with acute ischemic stroke (1-4). This increased blood pressure (BP) falls spontaneously within the first week after acute ischemic stroke without specific antihypertensive therapy (5). High BP in the early phase of acute ischemic stroke is a sign of a poor outcome associated with poor functional outcome and higher mortality (6-9). The mechanisms for these BP changes after stroke are still unclear, but may be related to stroke-induced changes in sympathoadrenergic activity (4,10), stress reaction to hospital admission or BP measurement (11), or central mechanisms (6). On the other hand, it is now accepted that elevated low-density lipoprotein (LDL)-cholesterol is an independent, modifiable risk factor for atherosclerotic cardiovascular disease (12). Recently, Edmunds et al. (13) demonstrated that malignant hypertension was associated with an abnormal lipid profile characterized by a significantly lower high-density lipoprotein (HDL)-cholesterol level and a tendency for higher LDL-cholesterol level after adjusting for confounding variables, compared to normotensive controls. We here present a study of the lipid profile in elderly patients admitted to our hospital with acute ischemic stroke associated with severe hypertension (>200/120 mmHg) within the first 72 hours of symptom onset. The results were compared with those in elderly patients with acute ischemic stroke associated with moderate hypertension (160-199/100-119 mmHg), and with normotensive and/or mildly-hypertensive (<160/100 mmHg) controls.

Department of Geriatric Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, kahoku, Ishikawa 920-0293, Japan
Correspondence: Shigeto Morimoto, M.D., Ph.D.
Accepted: February 8, 2011

METHODS

Subjects

Consecutive patients admitted to the Geriatric Emergency Ward of Kanazawa Medical University Hospital, a major urban hospital in Ishikawa Prefecture, with a diagnosis of ischemic stroke during 2002 to 2010 were recruited into the study. Patients