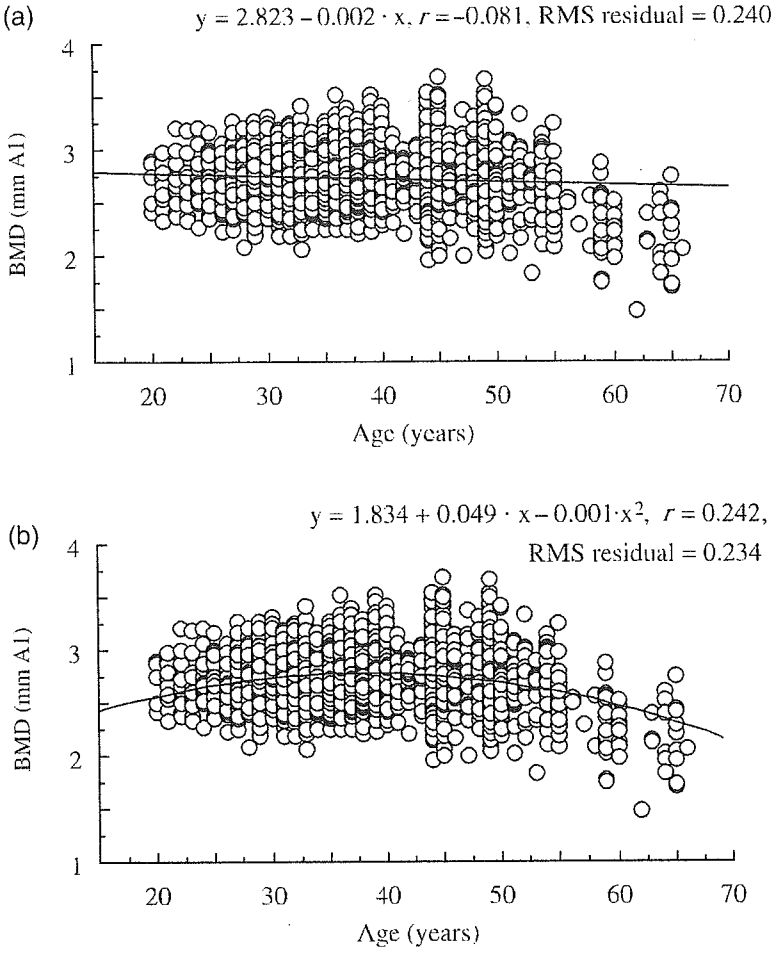


Figure 1. Relationship between BMD and age in premenopausal women as a function of simple (a) and polynomial (b) regression.

In the postmenopausal women, we examined various regression analyses for the relationship between BMD vs. age and YSM (Figure 2). As the result of a comparison of correlation coefficients among each regression, it was not found whether a nonlinear or linear function was suitable for postmenopausal women. In the nonlinear functions as determined by polynomial regression, overall partial coefficients of the YSM were significantly related to BMD, while a partial coefficient of age for the binomial variable was not significant. Therefore, the BMD of postmenopausal women plotted against the YSM instead of age is used hereafter. No significant regressions were obtained from the logarithm or exponential-function models.

In order to establish a prospective-change model of BMD both in pre- and postmenopausal women, we performed a stepwise regression analysis with age, YSM, height, weight, and BMI as independent variables. Table II shows the best-fit equations for the nonlinear and linear change models. For premenopausal women, the nonlinear-change model was applied for age as a binomial variable. For postmenopausal women, linear- and nonlinear-change models were used as well as a later model that included YSM as a binomial variable.

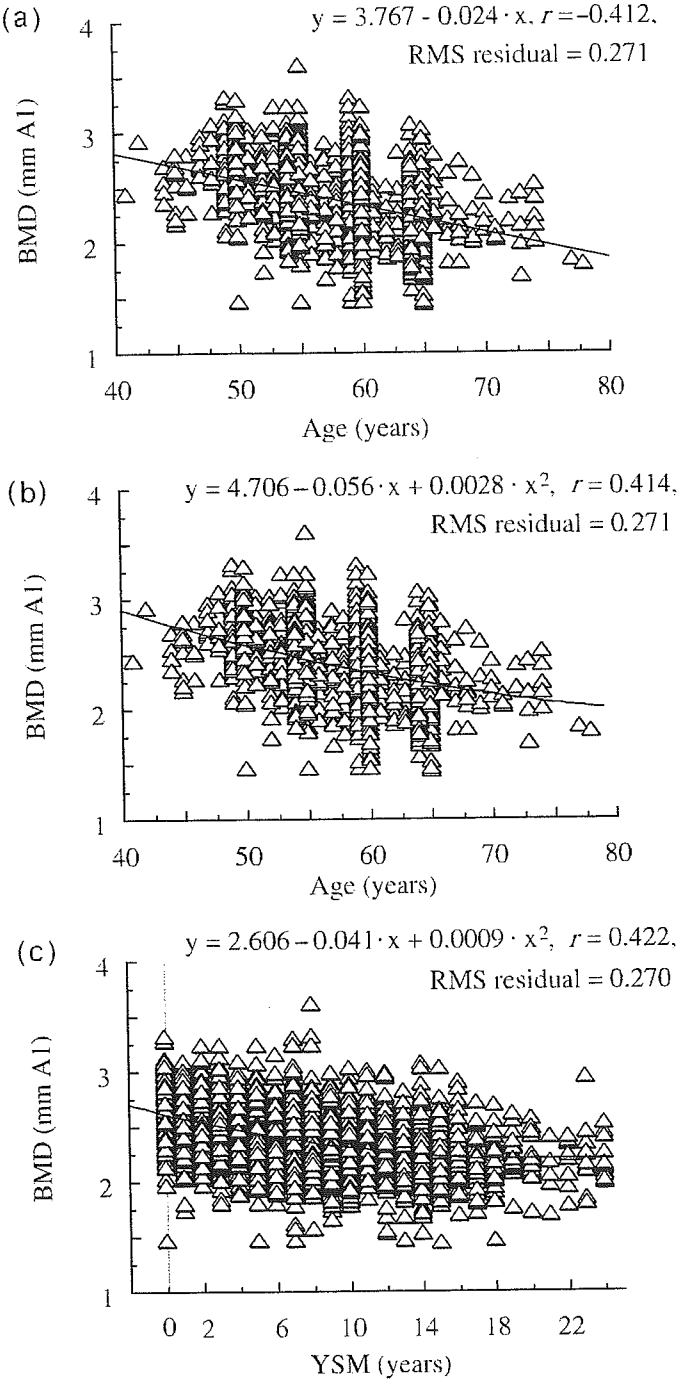


Figure 2. Relationship between BMD *vs.* age and years since menopause (YSM) in postmenopausal women. Simple regression for BMD with age (a). Polynomial regression for BMD with age (b) and with YSM (c).

Table II. Best-fit equations expressing BMD in cross-sectional population.

| | Equation | $r$ | RMS residual |
|---|---|---|---|
| Premenopause | $BMD = 1.0841 - 0.0006 \cdot age^2 + 0.0481 \cdot age + 0.0048 \cdot height$ | 0.262 | 0.233 |
| Postmenopause | | | |
| Nonlinear | $BMD = 2.4388 + 0.0008 \cdot YSM^2 - 0.0277 \cdot YSM - 0.0115 \cdot age + 0.0055 \cdot height$ | 0.446 | 0.266 |
| Linear | $BMD = 2.3908 - 0.0136 \cdot age - 0.0117 \cdot YSM + 0.0005 \cdot height + 0.005 \cdot BMI$ | 0.438 | 0.268 |

BMD, bone mineral density (mm Al); YSM, years since menopause; BMI, body mass index; RMS, root mean square.

*Changes in BMD: Longitudinal design*

The longitudinal data represented in Table III contains the means and standard deviations of BMD and physical characteristics at the baseline and 1-year follow-up. In premenopausal women, the BMD of the 40-year age group significantly decreased by 0.9% ($t(78) = 2.80$, $p < 0.01$), whereas the other age groups showed no BMD loss. In perimenopausal women, we found a statistically significant decrease of 3.2% ($t(13) = 2.78$, $p < 0.05$). In postmenopausal women, the BMD of the 1–5 and 6–10 YSM groups significantly decreased by 3.5% and 1.52% ($t(64) = 6.78$, $p < 0.001$; and $t(47) = 3.51$, $p < 0.001$), respectively. No significant BMD reduction was observed in the 11–15 YSM group.

*Validity of change model*

The annual percentage changes in BMD between the actual and predicted values of the longitudinal population are shown in Table IV. To compare the difference between the actual and predicted values in premenopausal women, the Wilcoxon signed-rank test was applied. The results showed no significant differences in any of the age groups.

In peri- and postmenopausal women, the Friedman test was used to compare the difference between the actual and predicted values for each of the YSM groups. Significant differences were found in all the groups: perimenopause, 1–5 YSM, 6–10 YSM, and 11–15 YSM ($\chi^2(2, n = 14) = 10.86$, $p < 0.01$; $\chi^2(2, n = 65) = 47.66$, $p < 0.001$; $\chi^2(2, n = 48) = 12.04$, $p < 0.01$; and $\chi^2(2, n = 47) = 17.53$, $p < 0.001$), respectively. A *post hoc* Steel–Dwass test showed that actual bone reductions were significantly underestimated by the nonlinear- and linear-change models at 1–5 YSM and 6–10 YSM, whereas the nonlinear-change model provided a closer estimate to the actual BMD changes (Table IV). In addition, the annual percentage rates of BMD loss with YSM decreased significantly both in actual and estimated values from the nonlinear equation ($F(3,170) = 7.47$, $p < 0.001$; and $F(3,170) = 24.00$, $p < 0.001$), whereas they increased significantly in values estimated from the linear equation ($F(3,170) = 4.99$, $p < 0.01$).

## Discussion

We found, in both cross-sectional and longitudinal data, that the BMD for premenopausal women increased slowly until age 40 and fell gradually after that. It is suggested that the changes in the metacarpal BMD of premenopausal women are characterized by three

Table III. BMD and physical characteristics of follow-up subjects at baseline and 1 year after.

| Groups | $n$ | Height (cm) | | Weight (kg) | | BMI ($kg\,m^{-2}$) | | BMD (mm Al) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | 1 year | Baseline | 1 year | Baseline | 1 year | Baseline | 1 year |
| Premenopause | | | | | | | | | |
| 20–29† | 21 | 158.6 ± 6.5 | 158.8 ± 6.5 | 53.5 ± 6.8 | 53.0 ± 7.2 | 18.44 ± 7.94 | 19.11 ± 6.72 | 2.639 ± 0.195 | 2.656 ± 0.179 |
| 30–39† | 75 | 159.0 ± 4.6 | 159.1 ± 4.6 | 51.4 ± 6.5 | 52.0 ± 6.7** | 15.57 ± 9.12 | 16.51 ± 8.67 | 2.700 ± 0.217 | 2.714 ± 0.243 |
| 40–49† | 79 | 154.8 ± 5.3 | 154.8 ± 5.4 | 53.9 ± 6.7 | 54.0 ± 6.7 | 22.50 ± 2.65 | 22.43 ± 2.63 | 2.754 ± 0.194 | 2.728 ± 0.195*** |
| 50–59† | 10 | 153.8 ± 2.3 | 152.8 ± 2.5 | 55.7 ± 8.7 | 55.9 ± 8.8 | 23.55 ± 3.67 | 23.96 ± 3.77 | 2.686 ± 0.189 | 2.676 ± 0.183 |
| Perimenopause | | | | | | | | | |
| YSM 0 | 14 | 154.2 ± 5.9 | 154.2 ± 6.2 | 50.6 ± 6.8 | 51.4 ± 7.1* | 21.25 ± 2.36 | 21.58 ± 2.46* | 2.845 ± 0.220 | 2.751 ± 0.190* |
| Postmenopause | | | | | | | | | |
| YSM 1–5 | 65 | 153.7 ± 4.7 | 153.7 ± 4.6 | 53.5 ± 6.6 | 53.8 ± 6.4 | 22.66 ± 2.72 | 22.78 ± 2.51 | 2.560 ± 0.264 | 2.468 ± 0.252*** |
| YSM 6–10 | 48 | 152.9 ± 5.5 | 153.0 ± 5.7 | 53.2 ± 6.9 | 53.1 ± 6.9 | 22.75 ± 2.85 | 22.79 ± 2.77 | 2.370 ± 0.251 | 2.333 ± 0.247*** |
| YSM 11–15 | 47 | 151.9 ± 4.4 | 151.7 ± 4.3 | 52.0 ± 7.4 | 52.4 ± 7.4 | 22.52 ± 3.14 | 22.77 ± 3.16 | 2.245 ± 0.208 | 2.234 ± 0.212 |

Values are means ± SD; †Age at baseline; YSM, years since menopause. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, baseline vs. 1 year.

Table IV. Annual changes in BMD (%) between actual and predicted values in longitudinal population.

| Groups | *n* | Actual | Nonlinear | Linear |
|---|---|---|---|---|
| Premenopause | | | | |
| 20–29† | 21 | 0.75 ± 3.45 | 0.61 ± 0.16 | – |
| 30–39† | 75 | 0.48 ± 3.78 | 0.25 ± 0.16 | – |
| 40–49† | 79 | −0.88 ± 2.88 | −0.26 ± 0.20 | – |
| 50–59† | 10 | −0.33 ± 2.88 | −0.69 ± 0.58 | – |
| Perimenopause | | | | |
| YSM 0 | 14 | −3.17 ± 4.57 | −1.47 ± 0.17 | −0.92 ± 0.16[c] |
| Postmenopause | | | | |
| YSM 1–5 | 65 | −3.50 ± 3.86 | −1.32 ± 0.26[a] | −0.97 ± 0.18[b,c] |
| YSM 6–10 | 48 | −1.52 ± 3.24 | −1.08 ± 0.19[a] | −1.02 ± 0.15[b] |
| YSM 11–15 | 47 | −0.46 ± 3.12 | −0.89 ± 0.52 | −1.11 ± 0.33[c] |

Values are means ± SD. †Age at baseline; BMD, bone mineral density; YSM, years since menopause. Significant differences between actual vs. nonlinear-model[a]; Actual vs. linear-model[b]; Nonlinear- vs. linear-models[c].

distinct phases: an initial increase in adolescence, stabilization at maturity, and a decline in old age. This pattern of changes in BMD is in agreement with previous research which measured the distal forearm (Nakamura et al. 2000), hand (Malkin et al. 2002), and metacarpal BMD (Matsumoto et al. 1994). Our main result for premenopausal women showed that the nonlinear-change model using the square of age, age and height as variables was beneficial in evaluating the actual metacarpal BMD variability. The fitted nonlinear function for age-related BMD changes is consistent with a previous study that found that the quadratic equation for age was best fitted to the forearm BMD changes in premenopausal women using a large sample (Luisetto et al. 1993). Although other studies have observed that BMD loss in the distal forearm is not age-related for premenopausal Caucasian women (Nuti and Martini 1993; Hansen 1994; Löfman et al. 1997), they only examined a relatively small sample size.

For postmenopausal women, regression analyses of cross-sectional data obtained two models of BMD variabilities with linear and nonlinear functions, and these depended on both YSM and age (see Table II). Most of the research examining postmenopausal women has shown BMD reduction occurring in conjunction with YSM (Gallagher et al. 1987; Bjarnason et al. 1995; Hansen et al. 1995; Warming et al. 2002). However, those studies used either YSM or age as a variable for the regression function to assess BMD differences. Nuti and Martini (1993), who applied multiple regression analysis, showed that BMD differences were affected by both YSM and age in healthy postmenopausal women. Therefore, it is valid to estimate the metacarpal BMD change model that is associated with both YSM and age.

In comparing the absolute changes in BMD with the predicted changes from longitudinal data by two prospective models, we found that the nonlinear-change model using the square of YSM, YSM, age and height as variables was adequate to estimate actual metacarpal BMD reduction rather than the linear-change model. Additionally, the annual percentage rates of BMD loss for the perimenopausal and 1–5 YSM groups were 3.2% and 3.5%, respectively. These rates were more than double the 1.5% of the 6–10 YSM group. This finding was similar to those in previous studies. Hansen et al. (1995) have shown in a 15-year follow-up study that the annual rates of decrease in forearm bone mineral content were around 3% the first 3 years after menopause and continued at around 1% until 15 YSM. Gallagher et al. (1987) have indicated that BMD loss occurs

as a logarithmic rather than a linear function, and that the annual rate of bone loss in the second postmenopausal year was 3.4%, 1.7% in the fourth year, and 0.8% in the ninth year. These studies support that the nonlinear function utilizing YSM is suitable in evaluating in metacarpal BMD loss for postmenopausals.

The present nonlinear-change model in BMD for postmenopausal women was able to express the decreasing trend of annual percentage rates, whereas this change model underestimated rates 10 years after menopause. Warming et al. (2002) compared the 2-year changes in BMD estimated from cross-sectional data with the actual longitudinal changes. They showed an agreement for the first decade after menopause, and disagreement for the period beyond 10 YSM, but chose to show only the simpler linear regression for age-related changes. In contrast, Melton et al. (2000) indicated that the cross-sectional data underestimated the bone loss actually observed longitudinally at the distal forearm site. In addition, some studies have indicated that a rapid rate of bone loss is observed in about one in three women within their early postmenopausal years (Hui et al. 1990; Nordin et al. 1993; Ross et al. 1994). In a cross-sectional study it is difficult to identify the determinants of individual changes if a rapid rate of bone loss occurs in a short period. As a consequence, the rates of BMD loss predicted by the change model underestimate the longitudinal rates of rapid bone loss. It is suggested that longitudinal data are needed to improve the evaluation of BMD variability in postmenopausal women. In addition, the present longitudinal study has limitation in terms of sample size, given that the follow-up subjects represented only 7% of the cross-sectional population. Further investigation with sufficiently larger samples must be undertaken to delineate more precisely the changes in BMD at different stages of life.

With regard to physical characteristics, stepwise regression analysis showed that the BMD differences were related to height in change models for pre- and postmenopausal women. There is also evidence of age- and height-related forearm BMD loss in healthy women (Seo et al. 1994; Melton et al. 2000). However, it remains unclear whether this relationship was due to an actual reduction in height over time or to an effect of secular changes. Although weight is well known to be a major determinant of bone mass (Nuti and Martini 1993), our results show that it has not been used as an independent variable in any change model. Since the metacarpal bone is a non-weight bearing site, it is likely that a mechanical-load effect is precluded.

## Conclusion

We found nonlinear-change models reflect BMD variabilities using age and height as variables in premenopausal women, and YSM, age and height in postmenopausal women. Our results indicated that the change model for premenopausal women might be useful for the estimation of individual BMD changes, but that the change model for postmenopausal women underestimated the actual rates of BMD loss in groups under 10 YSM. Further longitudinal studies will be needed to address the issue of long-term variability in the individual rate of bone loss for postmenopausal women.

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**Résumé.** *Arrière plan:* On accepte communément que les femmes âgées aient connu une perte de densité minérale osseuse (DMO) avec l'âge et la ménopause, cependant seulement

un petit nombre d'études ont utilisé un modèle de régression multiple, qui inclut des caractéristiques physiques afin de suivre de manière adéquate les changements de DMO au cours de la vie
*Objectif:* Une étude prospective a été menée afin de caractériser les modalités normales du changement de la DMO métacarpienne chez les femmes japonaises et pour estimer la possibilité d'appliquer un modèle d'ajustement utilisant des données transversales comparées avec la variabilité longitudinale.
*Sujets et méthodes:* L'étude consiste en sonnées transversales de 5422 femmes en bonne santé et d'un suivi d'un an pour 359 femmes. La DMO métacarpienne a été mesurée par densitométrie radiographique calculée par ordinateur. Des analyses de régression linéaires multiples et non linéaires, ont été effectuées sur les données transversales. Une analyse non paramétrique a été utilisée pour comparer les pourcentages de changement de DMO entre valeurs estimées et valeurs observées.
*Résultats:* Les données transversales indiquent que la meilleure équation ajustée est un modèle non linéaire employant les variables d'âge et de stature des femmes avant la ménopause, les années depuis la ménopause (ADM) et l'âge et la stature après la ménopause. Les résultats des données longitudinales indiquent qu'avant la ménopause, le changement en DMO est plus élevé dans le groupe d'âge 30–39 ans que dans le groupe d'âge 20–29 ans et ceux-ci sont inférieurs aux valeurs de des groupes 40–49 et 50–59 ans. Les taux annuels de changement de DMO que ce soit par les valeurs mesurées ou par les valeurs estimées sont similaires. Chez les femmes ménopausées, les changements en DMO observés indiquent que le rapide taux de réduction est supérieur à 3% entre 0 et 5 ans après la ménopause, puis de 1,5% entre 6 et 10 ans après la ménopause et décline à un rythme plus lent à partir de 11 ans après la ménopause. Le modèle de changement coïncide avec les changements en DMO observés chez les femmes ménopausées, tandis que les taux de perte de DMO du modèle sous estiment les changements effectifs entre 1 et 10 ans après la ménopause.

**Zusammenfassung.** *Hintergrund:* Es ist allgemein bekannt, dass bei älteren Frauen die Knochendichte (bone mineral density, BMD) im Alter und mit der Menopause abnimmt. Allerdings haben nur wenige Studien ein multiples Regressionsmodell benutzt, das körperliche Merkmale einschließt, um die komplexen Änderungen der Knochendichte im Verlauf des Lebens zu erfassen.
*Ziel:* Es wurde eine prospektive Studie durchgeführt, um das normale Muster von Mittelhandknochendichte-Änderungen bei Japanischen Frauen zu charakterisieren und um unter vergleichender Verwendung von Quer- und Längsschnittsdaten die Anwendbarkeit eines rechnerischen Anpassungsmodells zu prüfen.
*Probanden und Methoden:* Die Studie umfasste Querschnittsdaten von 5422 gesunden Frauen und eine Einjahres-Nachuntersuchung von 359 Frauen. Die Mittelhandknochendichte wurde radiologisch mittels Rechner-Densitometrie gemessen. Multiple lineare und nicht-lineare Regressionsanalysen wurden an den Querschnittsdaten durchgeführt. Eine nicht-parametrische Analyse wurde benutzt, um die prozentuale Veränderung der Knochendichte zwischen tatsächlich gemessenen und geschätzten Werten zu vergleichen.
*Ergebnisse:* Die Querschnittsdaten zeigten, dass die beste rechnerische Anpassung durch ein nicht-lineares Modell unter Verwendung der Variablen Alter und Körperhöhe bei Frauen vor der Menopause erzielt wurde, und unter Verwendung der Variablen Jahren seit der Menopause (years since menopause, YSM), Alter und Körperhöhe bei Frauen nach der Menopause. Die Ergebnisse der longitudinalen Daten zeigten folgendes. Bei Frauen vor der Menopause waren die tatsächlichen Knochendichteänderungen in der Gruppe

der 30–39-jährigen größer als in der Gruppe der 20–29-jährigen und geringer in der Gruppe der 50–59-jährigen als in der der 40–49-jährigen. Das prozentuale Ausmaß der jährlichen Veränderung der Knochendichte zwischen den tatsächlich gemessenen und den über das Anpassungsmodell geschätzten Werten war sehr ähnlich. Bei Frauen nach der Menopause zeigten die tatsächlich gemessenen Veränderungen der Knochendichte, dass die beobachtbare Abnahmerate der Knochendichte 0 bis 5 Jahre nach der Menopause größer als 3% war, 6 bis 10 Jahre nach der Menopause 1,5% betrug, und erst 11 Jahre nach Menopause langsamer wurde. Das rechnerische Anpassungsmodell zeigte zwar den Trend der tatsächlichen Knochendichteänderung bei Frauen nach der Menopause, unterschätzte allerdings die tatsächlichen Knochendichteänderungen in den ersten 10 Jahren nach der Menopause.

**Resumen.** *Antecedentes*: La pérdida de densidad mineral ósea (BMD) con la edad y en la menopausia está ampliamente reconocida en las mujeres ancianas. Sin embargo, muy pocos estudios han utilizado un modelo de regresión múltiple que tuviera en cuenta características físicas para evaluar los cambios globales que se producen lo largo de la vida en la BMD.
*Objetivo*: Se realizó un estudio prospectivo para caracterizar los patrones normales de cambio en la BMD de los metacarpos en mujeres japonesas y para estimar la aplicabilidad de un modelo ajustado, utilizando datos transversales comparados con la variabilidad longitudinal.
*Sujetos y métodos*: Se obtuvieron datos transversales de 5422 mujeres sanas y se realizó un seguimiento de 359 mujeres durante 1 año. La BMD de los metacarpos se determinó mediante densitometría de rayos X computerizada. Se realizaron análisis de regresión lineal y no lineal múltiple en los sujetos de la muestra transversal. Se utilizó un análisis no paramétrico para comparar las tasas porcentuales de los cambios en la BMD entre los valores reales y los estimados.
*Resultados*: Los datos transversales mostraron que la ecuación con el mejor ajuste era un modelo de cambio no lineal, que usaba como variables la edad y la estatura en las mujeres premenopaúsicas, y los años que habían transcurrido desde la menopausia (YSM), así como la edad y la estatura, en las mujeres postmenopaúsicas. Los resultados de los datos longitudinales indicaron lo siguiente: en las mujeres premenopaúsicas, los cambios reales en la BMD fueron mayores en el grupo de 30–39 años de edad que en el de 20–29 años, y menores en el grupo de 50–59 años que en el de 40–49. Las tasas de cambio anual de la BMD entre el valor real y el estimado por el modelo de cambio eran muy similares. En las mujeres postmenopaúsicas, los cambios reales en la BMD indicaban que la rápida tasa de reducción observada era superior al 3% a los 0–5 YSM y del 1,5% a los 6–10 YSM; posteriormente, mostraban una menor tasa de disminución a los 11 YSM. El modelo de cambio representaba la tendencia del cambio real en la BMD en las mujeres postmenopaúsicas, mientras que las tasas estimadas de pérdida de la BMD subestimaban los verdaderos cambios a los 1–10 YSM.

observed in other studies.[3–6] We attribute this result mostly to the older mean age of our cohort.[2]

Examining Perucchini et al.'s[1] sample, the mean age is higher (76.8, range 63–98) than that observed in our cohort, the overall tolerability was lower, and contrary to our[1] and other studies,[3–5] IV+PV was better tolerated than IV alone.

With the purpose of assessing the variation of incidence of adverse effects with age, we stratified the vaccinees into five age groups. As shown in Table 1, the incidence of adverse effects demonstrates a significantly decreasing trend with the increase in age, from 16.2% at aged 65 to 69 to 12.3% at age 85 and older chi-square ($\chi^2$) for trend $P<.001$).

The observed decreasing overall trend is significant in the IV+PV group (from 19.8% at 65–69 to 12.5% at $\geq$ 85; $\chi^2$ for trend $P<.001$) and remains significant for the local (from 15.2% at 65–69 to 9.6% at $\geq$ 85; $\chi^2$ for trend $P<.001$) and the systemic symptoms (from 7.8% at 65–69 to 4.3% at $\geq$ 85; $\chi^2$ for trend $P<.001$) (Table 1). Those receiving only IV did not show a significant variation in the incidence of adverse effects by age group.

Female subjects showed a higher reactogenicity than men (16.1 vs 13.1) and a significant decreasing trend in incidence of adverse effects by age (from 18.2% at 65–69 to 12.8% at $\geq$ 85; $P<.001$). The significant trend persisted when analyzing local symptoms (from 14.4% at 65–69 to 10.4% at $\geq$ 85, $\chi^2$ for trend $P<.001$) separated from the systemic ones (from 6.1% at 65–69 to 3.5% at $\geq$ 85, $\chi^2$ for trend $P<.001$).

In conclusion, we agree with Perucchini et al.[1] and other authors[3–8] that simultaneous administration of IV and PV is safe and well tolerated in older people.

The lower incidence of adverse effects observed in our investigation could be related to the older mean age of the subjects examined than in other studies[3–6] or to the shorter follow-up period.[1,7]

What does not convince us, and is contradictory to our and to other conclusions,[3–7] is the observation by Perucchini et al. that the incidence of adverse effects was higher in those receiving IV only than in those receiving IV+PV; only the limited size of their sample could explain this.

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## RECREATIONAL REHABILITATION IMPROVED COGNITIVE FUNCTION IN VASCULAR DEMENTIA

*To the Editor:* Dementia is a major problem in developed countries from the medical and economic points of view. Various nonpharmacological therapies for dementia, such as life review, reality orientation, behavioral treatment, sensory stimulation, music therapy, physical therapy, and occupational therapy, have been reported,[1–5] but there has been no study to suggest that nonpharmacological therapies can activate cognitive function itself in demented patients. We investigated whether recreational rehabilitation improves cognitive function in vascular dementia (VD) and Alzheimer's disease (AD).

Four hundred twenty-nine patients were admitted to the Comprehensive Geriatric Unit at the National Center of Geriatrics and Gerontology, Obu, Japan, between August 1, 1998, and December 31, 1999. The 267 patients who were diagnosed as nondemented were excluded. Demented patients with complications such as pneumonia (n = 18), acute heart failure (n = 14), gastrointestinal disease (n = 12), acute stroke (n = 11), dehydration (n = 6), fractures (n = 4), orthopedic disease without fracture (n = 4), respiratory disease without pneumonia (n = 4), urinary tract infection (n = 2), and other disease (n = 5) were also excluded. Consequently, the subjects in this study were 37 patients with AD (11 men and 26 women) and 45 patients with VD (13 men and 32 women). The demented patients were treated with recreational rehabilitation alone, including playing board games, doing crafts, playing musical instruments, playing balloon volleyball, and dancing. Recreational rehabilitation was performed 5 days a week from Monday to Friday in the meeting room of the Comprehensive Geriatric Unit. One occupational therapist and one nurse organized a 90-minute therapy session for about 10 patients. To determine whether recreational rehabilitation improves cognitive function in demented patients, Mini-Mental State Examination (MMSE[6]) scores were measured before and after recreational rehabilitation.

Age, female:male ratio, Katz index of activities of daily living, physical self-maintenance scale,[7] morale scale, and MMSE before recreational rehabilitation were not different

Table 1. Cognitive Function Before and After Recreational Rehabilitation in Alzheimer's Disease and Vascular Dementia

| | Mini-Mental State Examination Score | | |
|---|---|---|---|
| | Before | After | |
| Subjects | Mean ± Standard Deviation | | *P*-value |
| Alzheimer's disease (n = 37) | 14.5 ± 6.6 | 14.9 ± 6.6 | .35 |
| Vascular dementia (n = 45)* | 13.5 ± 5.1 | 15.0 ± 5.5 | .004 |
| ≧30 sessions (n = 15)* | 14.3 ± 4.9 | 16.7 ± 5.2 | .008 |
| 18≦ < 30 sessions (n = 15) | 13.9 ± 4.9 | 14.8 ± 5.9 | .28 |
| < 18 sessions (n = 15) | 12.3 ± 5.6 | 13.4 ± 5.1 | .27 |

*Statistically significant.

between VD and AD. MMSE scores did not improve in patients with AD with recreational rehabilitation ($P = .35$) but improved significantly in patients with VD ($P = .004$) (Table 1). According to the frequency of treatments, these patients with VD were divided into the following three groups of 15 patients each (< 18 sessions, 18≦ < 30 sessions, and ≧30 sessions). Of the three subgroups of VD, the most frequently treated group showed a significant improvement ($P = .008$), whereas the other two subgroups did not.

Previous cross-sectional studies have reported associations between dementia and reduced participation in leisure activities in midlife, as well as between cognitive status and participation in leisure activities in old age.[8,9] A recent paper reported that leisure activity might prevent the occurrence of new dementia.[10] The rationale was that participation in leisure activities might increase cognitive reserve, delaying the clinical or pathological onset of dementia. The present study demonstrated that recreational rehabilitation did not improve cognitive function in AD but did in VD and that the most frequently treated group of the three subgroups of VD showed significant improvement, whereas no improvement was seen in the less-frequent groups. These findings clearly suggest that frequent recreational rehabilitation is an effective therapy for the cognitive function in VD.

In our preliminary study, single photon emission computed tomography using N-isopropyl-p-$^{123}$I idoamphetamine was performed in 11 patients with VD who were treated with recreational rehabilitation. These patients were initially divided into two groups based on changes in MMSE scores during recreational rehabilitation. The improved group (6 of 11 patients) had a gain of 3 or more points in MMSE scores, and the no-improvement group (5 of 11 patients) had a gain of 2 points or less. The improved group showed a significantly greater decrease in cerebral blood flow in the frontal region than the no-improvement group ($P < .05$). The no-improvement group showed a remarkably patchy decrease of blood flow in all regions ($P < .001$). In the present study, these findings suggested that cognitive function in patients with a frontal reduction using assessment of cerebral blood flow might improve more than in patients with a patchy decrease in blood flow. The explanation for our findings is not clear. One explanation might be that the recreational rehabilitation increased cerebral blood flow in the prefrontal region: activation of the cognitive function may occur if cerebral blood flow in the prefrontal lobe is lower at rest than in all regions.

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特集
高齢者の歩行障害
Geriat. Med. 43(1) : 67~72, 2005

# 転倒・骨折予防のプログラム

原田　敦*　長屋　政博**

KEY WORD
骨粗鬆症
転倒予防
骨折予防
運動療法
ヒッププロテクター

POINT
■当院では，転倒による骨折を予防する診療システムとして，1つの外来で骨粗鬆症リスクと転倒リスクの評価と介入を行う体制を立ち上げた．
■骨粗鬆症リスクには骨粗鬆症治療(骨吸収抑制薬投与など)，転倒リスクには転倒予防介入(転倒予防教室)を行う．
■当院で行っている転倒予防教室での筋力強化およびバランス訓練を主体とした運動プログラムについて概説した．
■両介入でも対応できないような施設入所レベルの要介護高齢者で，まだ寝たきりにはなっていない者にはヒッププロテクターを考慮する．

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## はじめに

高齢者の骨折のうちで，脊椎骨折は転倒が関与せずに発生するものが少なくなく，その73％は自覚症状のない，レントゲンで初めて診断される形態的骨折とされ[1]，入院や手術などの必要はないため，その臨床的意義は少ない．かたや，転倒によって生じる骨折は，大なり小なり，疼痛という急性症状が伴って，否応なくADLも低下するため，医療機関での治療や介護施設での療養を余儀なくされることが多い．大腿骨頸部骨折がその代表である．このように転倒による骨折の臨床的意義は，形態的骨折より明らかに大きく，高齢化社会を迎えてその予防の必要性が高まっており，どのような診療体制が転倒による骨折の予防に有効であるかが問われている．現段階でわれわれの施設は，まだその解答を出せるような状況にはないが，最近始まったばかりの診療体制を紹介する．

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## 骨粗鬆症外来と転倒予防外来の融合

高齢者の骨折の原因となる病態は骨粗鬆症と転倒である．前者は骨の量と質の低下によって骨強度が下がり，骨折の準備状態を形成する．後者は，脆弱性の進んだ骨が実際に骨折する直接の契機となる．したがって，転倒による骨折を予防しようとするプログラムにおいては，骨粗鬆症と転倒に対する評価と介入が対等に同時進行で行われることが必要で，骨粗鬆症医学と

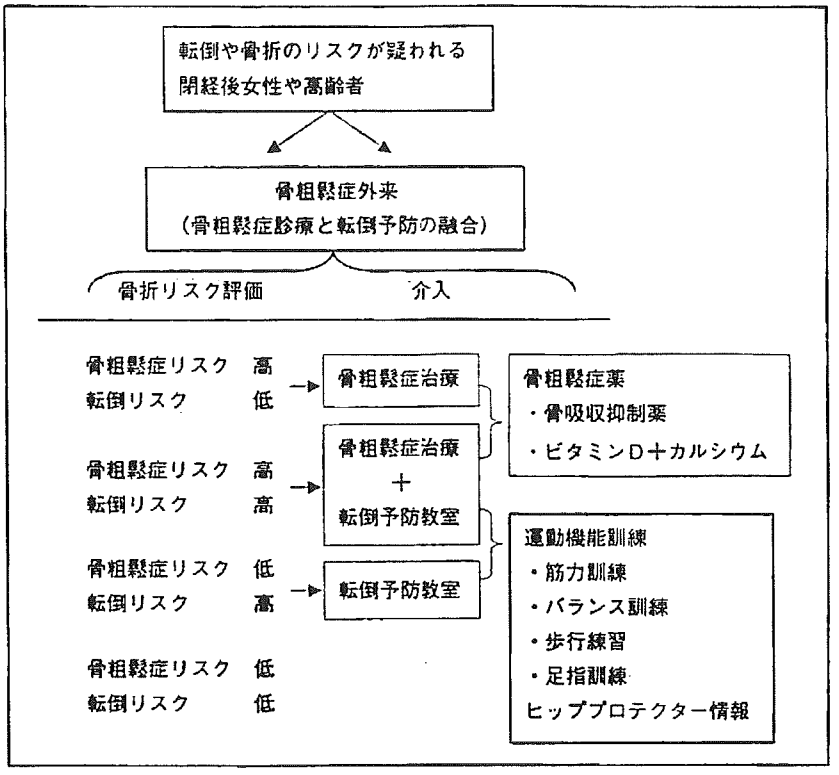


図1　骨折予防診療の流れ

転倒予防医学が車の両輪として機能するプログラムが求められるところであろう.

われわれの病院では, そのようなシステム構築への足がかりとして, 最近, 骨粗鬆症外来と転倒予防外来のドッキングのような診療システムの変更を行った. 従来, 当施設では骨粗鬆症外来は整形外科および内分泌内科の医師によって行われ, 転倒予防外来はリハビリテーション科医師によって担当され, 両者は独立した診療を行っていた. しかし, 前述したような理由を強く感じるようになったため, 両者を融合させるべく, 骨粗鬆症外来の担当医師を整形外科, 内分泌内科, 婦人科, リハビリテーション科に拡大して, その診療内容を骨粗鬆症による骨折リスクと転倒による骨折リスクの両方に対する評価と対策を盛り込んだ形にした(図1). このような診療システムの命名は, 本来なら転倒・骨折予防外来となるべきと考えられたが, 一般患者への普及がまだ十分でないと思われたので, 現時点では骨粗鬆症外来の呼称を用いている.

骨粗鬆症外来では, 表1のような転倒・骨折リスクの評価を多岐にわたって施行する. その結果, 骨密度と脊椎レントゲンによる原発性骨粗鬆症の診断基準[2]に基づいて, 骨粗鬆症と診断されれば, 骨粗鬆症治療介入を行う. 一方, ふらつきや転倒既往など, 転倒リスク[3,4]が高いと判断されれば, 転倒予防教室へ紹介して介入を行う. 両方のリスクを合併する場合は, 骨粗鬆症治療と転倒予防教室の両方を施行する(図1).

骨粗鬆症の治療選択は, 後期高齢期, あるいは骨折既往があるなど, 骨折リスクの高度な者や, 予防骨折部位として脊椎骨折だけでなく大腿骨頸部骨折を考える者にはアレンドロネートやリセドロネートなど, ビスホスホネートの強力な骨吸収抑制薬を使用し, 閉経後から前期高齢期までの年代, あるいは骨折既往がないなど, 骨折リスクが中等度で予防骨折部位として脊椎骨折だけを考える者には, ラロキシフェンなど

表1　骨粗鬆症と転倒のリスク評価

| 評価項目 | | 骨粗鬆症リスク | 転倒リスク |
|---|---|---|---|
| 身体基本情報 | 年齢 | ○ | ○ |
| | 身長，体重，閉経年数，出産数，喫煙 | ○ | |
| | 現在の運動 | | ○ |
| 転倒・骨折既往 | 脊椎骨折，その他の骨折 | ○ | |
| | 転倒 | | ○ |
| 既往歴・合併症 | 不整脈，起立性低血圧 | | ○ |
| | 高血圧，高脂血症，脳出血，脳梗塞 | ○ | |
| | 心不全，虚血性心疾患 | ○ | ○ |
| | 脳循環不全，一過性脳虚血発作 | | ○ |
| | 硬膜下血腫 | | ○ |
| | パーキンソン症候群 | ○ | ○ |
| | 痴呆 | ○ | ○ |
| | 脊髄後索障害，末梢神経障害，小脳障害，てんかん発作 | | ○ |
| | 骨関節炎，関節リウマチ | | ○ |
| | ミオパチー | | ○ |
| | 白内障，屈折異常，眼鏡不適合，緑内障 | | ○ |
| | 1型糖尿病 | ○ | |
| | 2型糖尿病 | ○ | ○ |
| | 甲状腺疾患，性線機能不全，クッシング症候群，卵巣摘出術，胃切除後，逆流性食道炎，肝障害，胃潰瘍，腎不全 | ○ | |
| | 喘息 | | |
| 使用薬剤 | 睡眠薬，精神安定薬，抗不安薬，抗うつ薬，その他の抗精神薬，降圧利尿薬，その他の降圧薬，血管拡張薬，非ステロイド鎮痛消炎薬，強心薬，抗パーキンソン病薬，鉄剤 | | ○ |
| | ステロイド薬 | ○ | |
| | 骨粗鬆症 | ○ | |
| 家族歴 | 母の骨折歴 | | ○ |
| 骨密度 | 腰椎，大腿骨，全身骨 | ○ | |
| 脊椎X線 | 胸椎，腰椎 | ○ | |
| 血液検査 | Ca，P，骨吸収マーカー，骨形成マーカー | ○ | |
| | PTH，1,25(OH)$_2$D，TSH，Free T$_3$ | ○ | |
| 運動機能 | 握力，膝伸展力，開眼片足立ち，最大1歩幅，10 m歩行速度 | | ○ |

マイルドな骨吸収抑制薬を使用する．いずれの場合でも，ビタミンDやカルシウムの不足がある者にはビタミンD剤とカルシウム剤併用などの補充治療を行う．

## 転倒予防プログラム

転倒予防教室のシステムは，全部で8週間のコースからなり，第1週に運動機能評価を行い，週1回5週にわたる転倒予防を目的とした運動を指導し，第7週に運動機能の再評価を行い，最後の週に評価内容の説明と今後の自宅での運動および生活指導を行うシステムである(図2)．運動機能の評価としては，転倒および日常生活に関する問診，大腿四頭筋筋力，大腿四頭筋での反応時間，重心動揺，握力，10 m歩行時間

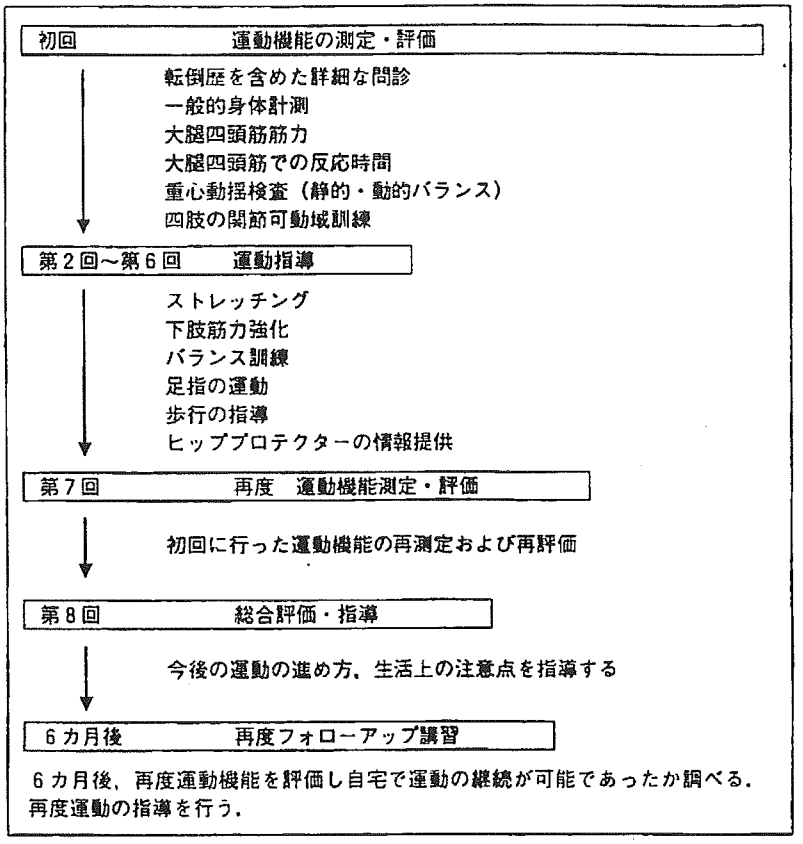


図2　国立長寿医療センターにおける「転倒予防教室」のシステム

などを評価している．

転倒予防教室の具体的な訓練内容は，ストレッチング訓練，下肢筋力の強化，歩き方の練習，自宅でもできる体操の指導，ビーダマを足指でつかんだり，裸足でタオルを巻取ることによる足指の練習，バランス訓練，片足立ち，ボール訓練などである．下肢筋力強化としては，2回目に座位で可能な重垂バンドやテラバンドを用いた練習を行う(図3)．また，同じ日に転倒の現状，原因を理解してもらう講習も行う．3回目には，ストレッチ運動と，棒体操を指導する(図4)．また，同じ日に転倒によって生じる骨折，運動の必要性について講習する．4回目にはバランス訓練を指導する．バランス訓練としては，片足立ちおよびつま先立ちの練習などがある．また，継ぎ足歩行の練習，立位にてできるだけ大きく側方・前方へのステッピング，端座位でできるかぎり離れた位置に手をついてもどる練習，四つ這い位で上下肢の挙上運動などを行う．また，ボールをつかった遊びも取り入れている．また同じ日に，歩行の指導として，前を向いて腹を軽くしめて，歩幅を広くとるように歩き，踵から着地し，足先で地面を蹴るように歩くように指導している．第5回目には，自宅でできる，あまり道具を用いないで可能な運動を指導する．また同じ日に，杖やシルバーカーなどの歩行補助具について講習を行う．6回目は，今まで指導してきた運動を自宅で行えるか復習を行う．7回目には再度運動機能評価を行い，転倒予防教室の効果を判定する．8回目には，再評価の結果について説明し，今後自宅で運動を続けることを指導する．そして6カ月後に来院していただき，運動機能の再評価と転倒の有無，運動の継続について問診し，再度

図3　座位での下肢筋力強化

図4　棒体操

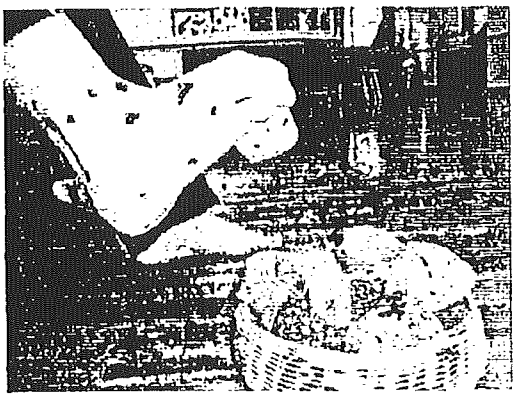

図5　足の指の運動

運動指導を行う．以上が当院で行っている転倒予防教室のシステムおよび運動プログラムである．

当院での転倒予防教室の効果としては，大腿四頭筋での反応時間の短縮，10 m 歩行時間の短縮，大腿四頭筋や握力の筋力増強が認められている．転倒予防を目的とした運動療法により，歩行機能の改善を認めた．しかしながら，転倒しやすい虚弱高齢者では，運動機能に個人差が大きく，また運動機能以外にも転倒に関与する因子が多いため，一律の運動指導を行うよりも，この転倒予防教室で行っているように対象者ごとの運動機能を評価して，個人の運動機能に適合した運動を指導することが必要であると考えている[5-7]．

## ヒッププロテクターの使用について

最後にヒッププロテクターについて述べる．この手段は介護現場で使用されるもので，これまで記述したような介入を外来通院で続けることが可能な自立度を保持している高齢者には，情報としてヒッププロテクターの説明はするが，その実際の適応は少ない．逆に，施設入所レベルの要介護高齢者でまだ寝たきりにはなってい

ない者は，転倒・骨折リスクが極めて高いにもかかわらず，骨粗鬆症治療や転倒予防介入で対応できない，あるいは間に合わないことが少なくなく，その場合はヒッププロテクターの使用が可能となる．本人任せにせず，介護者が協力してコンプライアンスさえ保てば大腿骨頸部骨折の半減を期待できる[8]．

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SHORT COMMUNICATION

# Positron emission tomography and magnetic resonance imaging in spinocerebellar ataxia type 2: a study of symptomatic and asymptomatic individuals

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Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant neurodegenerative disorder characterized as an expanded CAG trinucleotide repeats in SCA2 gene resulting in abnormal polyglutamine sequence. We used positron emission tomography (PET) and magnetic resonance imaging (MRI) to clarify metabolic and atrophic changes of the brain in two symptomatic and three asymptomatic individuals who were genetically confirmed for SCA2. PET revealed decreased glucose metabolism in both patients and two of the three asymptomatic carriers in the cerebellum, pons, or both. No PET abnormality was found in the remaining one carrier who had only a very mildly expanded CAG repeat. MRI showed cerebellar and/or pontine atrophic changes in both patients and one of three carriers. The present study suggest that hypometabolism and atrophy of the cerebellum and pons may occur years before the clinical onset of SCA2. PET and MRI may be useful in the early detection of subclinical brain changes associated with SCA2.

## Introduction

Autosomal dominant spinocerebellar ataxia type 2 (SCA2) is characterized by a progressive gait and limb ataxia, dysarthria, slow saccadic eye movements, supranuclear ophthalmoplegia, and depressed or absent tendon reflexes (Imbert *et al.*, 1996; Sanpei *et al.*, 1996; Stevanin *et al.*, 1996; Cancel *et al.*, 1997; Ueyama *et al.*, 1998). A CAG trinucleotide-repeat expansion within the coding sequence of SCA2 gene has been characterized as the disease-causing mutation (Imbert *et al.*, 1996; Sanpei *et al.*, 1996; Stevanin *et al.*, 1996). The CAG-repeat length is positively correlated with an early onset of the disease and severe clinical manifestations (Cancel *et al.*, 1997; Ueyama *et al.*, 1998). The SCA2 gene mutations may be responsible for a subset of familial parkinsonism (Gwinn-Hardy *et al.*, 2000; Shan *et al.*, 2001).

Several radiological studies, particularly those using magnetic resonance imaging (MRI), have demonstrated atrophic changes of the cerebellar hemispheres and pons in SCA2 patients (Klockgether *et al.*, 1998; Giuffrida *et al.*, 1999). However, MRI findings in asymptomatic SCA2 gene carriers have not been reported. Whilst MRI investigations basically represent a morphologic analysis, positron emission tomography (PET) clarifies pathophysiologic and metabolic characteristics, and various movement disorders such as Huntington's disease, Parkinson's disease, and progressive supranuclear palsy have been studied. Diminished brain glucose metabolism of the cerebellum has been shown in SCA type 3, i.e. Machado–Joseph disease (Soong *et al.*, 1997; Taniwaki *et al.*, 1997; Soong and Liu, 1998) and in SCA type 6 (Soong *et al.*, 2001). However, to the best of our knowledge, the metabolic characteristics in the brains of SCA2 individuals, symptomatic or asymptomatic, have not been described. In this study, we performed PET and MRI on symptomatic and asymptomatic SCA2 subjects with mutated SCA2 genes, and analyzed metabolic and atrophic changes detected in the brain regions.

## Patients and methods

### Subjects and genetic analysis

Two SCA2 patients (cases 1 and 2) and three asymptomatic male SCA2 gene carriers (cases 3–5) were entered in this study (Table 1). Informed written consent was obtained from all the subjects for the present study. Using genomic DNA of peripheral leukocytes, CAG-repeat expansion in the SCA2 gene was assessed by the polymerase chain reaction according to the method described elsewhere (Sanpei *et al.*, 1996). To accurately assess the CAG repeats, the amplified products were electrophoresed in a 8% denaturing polyacrylamide sequencing gel in an automated DNA sequencer. The

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Table 1 Clinical, genetic, PET and MRI data of symptomatic and asymptomatic SCA2 individuals

| Case | Sex/age (years) | Age at onset (years) | CAG repeats | Symptoms | PET | | MRI | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cerebellum[a] | Pons[b] | Cerebellum[c] | Pons[d] | Fourth ventricle[e] | Cerebellar area[f] |
| 1 | F/46 | Yes | 44 | 41 | 0.49[g] | 0.45[g] | 0.65[g] | 0.17[g] | 0.16[g] | 2779[g] |
| 2 | M/43 | Yes | 40 | 39 | 0.53[g] | 0.48[g] | 0.68[g] | 0.22 | 0.16[g] | 3530 |
| 3 | M/19 | No | - | 44 | 0.64[g] | 0.53 | 0.73 | 0.20 | 0.17[g] | 3881 |
| 4 | M/15 | No | - | 45 | 0.62[g] | 0.38[g] | 0.69 | 0.22 | 0.056 | 3562 |
| 5 | M/49 | No | - | 36 | 1.03 | 0.79 | 0.71 | 0.24 | 0.089 | 4155 |

Normal ranges (mean ± 3 SD) for [a,b]PET and [c–f]MRI parameters are 0.65–1.25, 0.49–0.86, 0.69–0.80, 0.20–0.29, 0.041–0.15, and 3342–4929 $mm^2$, respectively.

[g]Outside the normal range.

number of expanded CAG repeats of the SCA2 gene was 41, 39, 44, 45, and 36 in cases 1–5, respectively (Table 1), and all five subjects were found to possess pathogenic SCA2 gene according to the established criteria: normal, ≤31 repeats; 32–35, borderline; and ≥36, pathogenic (Payami *et al.*, 2003).

### Brain PET investigations

The PET imaging device (PCT-3600 W; Hitachi Medical, Tokyo, Japan) had an axial resolution of 5 mm and an in-plane resolution of 6.5 mm at the center of the field of view. PET imaging was performed 55 min after injection of 300 MBq of fluorodeoxyglucose F-18 (FDG). The region of interest (ROI, a 10 mm × 10 mm square) was determined in each brain region by reference to an atlas of axial tomography. Extreme caution was taken in the placement of ROI to avoid potential contamination from adjacent anatomical structures. Data were collected from the ROI, which were centered over a local peak in FDG metabolism in the frontal cortex, cerebellar hemispheres, and pons. Uptake of FDG was calculated from the radioactivity, and normalized regional uptake ratios were then calculated from the radioactivity of the cerebellar hemispheres and pons, divided by the activity in the frontal cortex. The frontal cortex was selected as the reference region for normalization because radiological (Giuffrida *et al.*, 1999) and histologic (Iwabuchi *et al.*, 1999) studies have shown that it is not affected in early and intermediate stages of the disease. The normal range of FDG consumption was calculated from the PET data from 12 normal controls (eight men and four women, age 40–72 years), and was determined as mean ± 3 SD.

### Brain MRI investigations

Brain MRI was performed with a 1.5-T device (GYROSCAN ACS-NT POWERTRAK3000; Philips, Tokyo, Japan) immediately after PET. The section thickness was 6 mm. We measured the following four parameters on the transverse T1-weighted spin echo images: (no. 1) transverse diameter of the pons, (no. 2) transverse diameter of the cerebellum, (no. 3) transverse diameter of the fourth ventricle, and (no. 4) the area of the cerebellum (Murata *et al.*, 1998). These parameters were quantified using standard image analysis software (NIH image). To adjust for individual variations, parameter nos 1–3 were expressed as a ratio relative to the maximum transverse diameter of the inner skull, with the normal range (mean ± 3 SD) being calculated from MRI data from 20 normal individuals (13 men and seven women, age 24–56 years).

## Results

### Clinical findings

Cases 1–5 were from a large Japanese family. The symptoms of cases 1 and 2 were typical for SCA2, showing cerebellar ataxia, slow saccades, and hyporeflexia (their grandfathers were brothers). The mother and an elderly sister of case 2 had ataxia which had manifested during their forties. Cases 3 and 4 were sons of the patient of case 1. Cases 3–5 were neurologically normal. The mother of case 5 (76 years old) had shown mild ataxia since she was 68 years old. No cases showed parkinsonism.

### Brain PET investigations

We investigated FDG consumption in the cerebellum and pons by PET. As shown in Fig. 1A and Table 1, regional hypometabolism in the cerebellum and pons was recorded in both SCA2 patients (cases 1 and 2). Hypometabolism was also found in two of the three asymptomatic carriers (cases 3 and 4): case 3 showed decreased FDG consumption in the cerebellum and pons, and case 4 showed hypometabolism in the

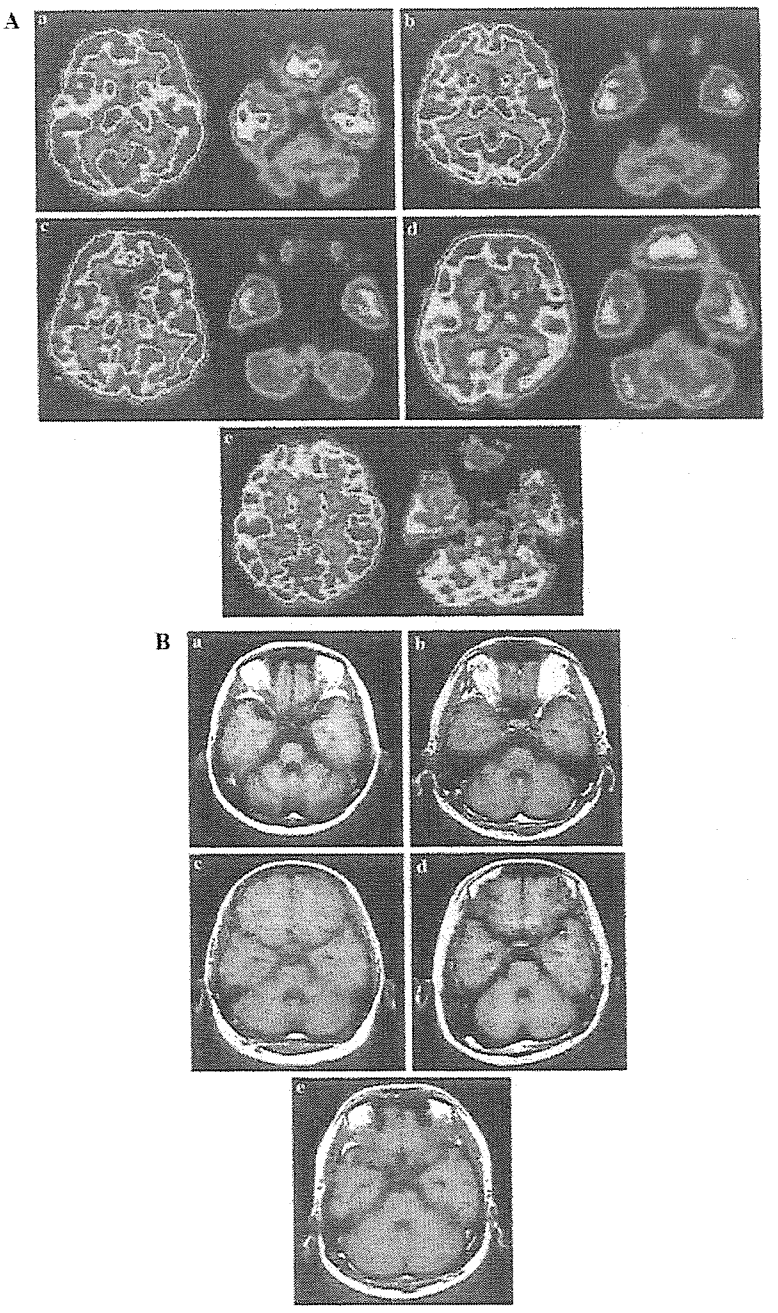

**Figure 1** PET (A) and MRI (B) studies of individuals with mutated SCA2 gene. (a–e) Correspond respectively to cases 1–5 (cases 1 and 2, SCA2 patients; cases 3–5, asymptomatic carriers). (A) PET study shows cerebellar and or pontine hypometabolism in cases 1–4 (a–d) and no significant hypometabolism in case 5 (e). (B) MRI study shows cerebellar and/or pontine atrophy in cases 1–3 (a–c) and no significant atrophy in cases 4 and 5 (d and e).

cerebellum. No apparent hypometabolism was detected in the remaining case (case 5) who had very mild expansion of CAG repeats of SCA2 gene.

### Brain MRI investigations

Four parameters – diameters of the cerebellum, pons, and fourth ventricle, and the area of the cerebellum were used for MRI evaluation of the brain atrophy. As shown in Fig. 1B and Table 1, case 1, a symptomatic patient, showed apparent atrophy, as determined by all four parameters. Case 2, the other symptomatic patient, showed decreased cerebellar diameter and increased fourth ventricle diameter. Amongst the three asymptomatic carriers, case 3 showed enlarged fourth ventricle although the other three parameters were normal.