

Fig. 2. Representative lateral cephalometric x-ray profiles in a patient before and after dental adjustment treatment.

Two rings show the external auditory meatuses of both sides. Zero mm of the dens is shown as a rectangular cross point (center). Before treatment, the occlusal plane shifted upwards by 9 mm on the right and 7 mm on the left side from the center of the dens (A). After dental adjustment treatment, the occlusal plane passed through the dens (B) and clinical symptom scores were reduced from 82 points to 19 points.

facet irritation or restriction result in peripheral entrapment neuropathies (Kopell and Thompson 1976). One common entrapment is the greater or lesser suboccipital nerves that pass between the occiput and atlas (Jones 1984). This may cause headaches or pain in the facial region. Many dental teams investigated and treated maloccluded teeth providing ideal dental occlusion by acrylic

overlay fillings placed on all mandibular and maxillary first and second molars, and observed relief of clinical symptoms (Costianes 1983; Fonder 1989; Alonen 2002). However, they did not adjust the occlusal plane to the center of the dens of the axis of cervical vertebrae. According to this procedure, the rotating force of the neck would be most effectively applied to the dens but not to the other cervical vertebrae. In the present study, we have shown that patients who visited dentists due to dental problems as well as physical symptoms demonstrated significantly higher frequency of shifts from the center of the DAV compared with healthy subjects. This report will be the first which proved that an adjustment of the MOP crossing the DAV would be effective in reducing physical symptoms associated with dental deformities.

A very complex structure and functions are found in the oral cavity. Considering mastication of foods as an example, a strong force is generated on the occlusal plane daily and it is natural to assume that even a slight inefficiency causes an accumulated load. In addition to the concept that the teeth are aligned neatly, if the occlusal plane is corrected to pass through the near center of the dens, the dens supports the neck to avoid shifts by minimizing the loads in the right and left side of the neck during mastication of food and, as a result, a stable neck may be obtained.

However, a precise mechanism for the effect of correction of MOP on physical symptoms such as headache or shoulder stiffness was not clarified in the present study. It might or might not be that all known mammals have an occlusal plane almost passing through the 1st and the 2nd cervical vertebrae, which might be very important in making the cervical vertebrae stable. In the future, it is necessary to find out whether the same phenomenon occurs in mammals or to prove the phenomenon by measuring the loads of the forces to the vertebrae. The present method demonstrated an initial step in showing a direction of the correction of the dental occlusal plane. There are many elderly people with dentures who complain of the unpleasant feeling of dentures, which might be caused by not being aware of an inadequate

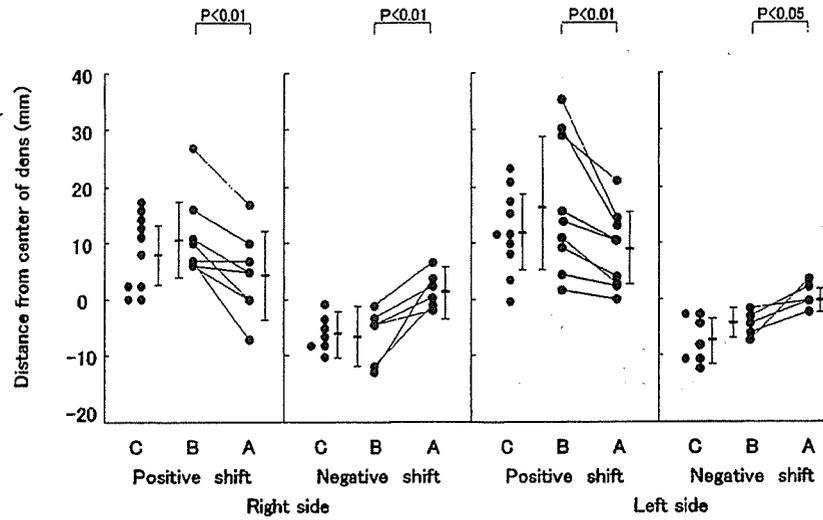


Fig. 3. The actual distance from the maxillary occlusal plane to the center of the dense. The vertical bar indicates the actual distance from the maxillary occlusal plane to the center of the dens. Data were obtained from patients without dental adjustment treatment (C), those from patients with dental adjustment treatment before (B) and after treatment (A) in either right or left side. A connected line means that the data corresponds to the same patient before and after treatment. Mean  $\pm$  s.d. are indicated by the bold horizontal bars and thin vertical bars, respectively. There was no significant difference between group C and B. There were significant differences between B and A ( $p < 0.01$  or  $p < 0.05$ ) as shown in this figure.

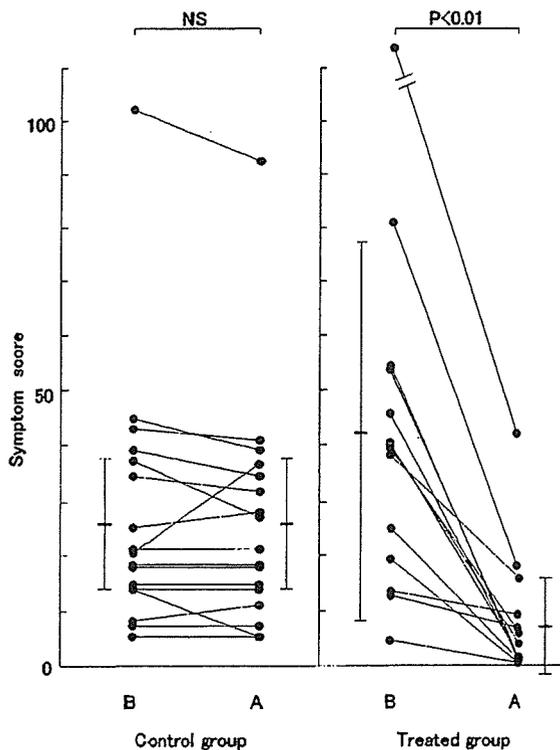


Fig. 4. Symptom scores in the control group and in the treated group, before and after dental treatment. Symptom scores are shown in patients with only caries treatment (Control group) and with both dental caries and adjustment treatments (Treated group) before (B) and after (A) treatment. A connected line means that the data corresponds to the same patient. There was no significant difference between symptom scores obtained before and after treatment in the control group ( $p = 0.86$ ). Symptom scores after treatment were significantly decreased compared with those before treatment in the treated group ( $p < 0.01$ ). The highest score before treatment in the treated group was 142 points, and this decreased to 42 points after treatment.

maxillary occlusal plane. It is suggested that for elderly people with dentures it should also be determined if they have an adequate MOP passing through the center of the DAV.

In conclusion, our results suggest that correction of the maxillary occlusal plane passing through the near center of the dens of the cervical vertebrae might be effective in relieving clinical symptoms associated with dental deformities.

### Acknowledgments

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In this case, the diagnosis of insulinoma was made in the examination of recurrent falls, and suspected because the falls always occurred after an overnight fast but in the absence of any other symptom. Also, the patient was alert and did not give the impression of frailty so often seen with recurrent falls. A careful history can identify unusual but treatable causes of recurrent falls.

Olivier Beauchet, MD, MS  
 Reto W. Kressig, MD  
 Ulrich M. Vischer, MD  
 Department of Rehabilitation and Geriatrics  
 Thomas de Perrot, MD  
 Department of Radiodiagnostics  
 Philippe de Saussure, MD  
 Division of Gastroenterology  
 Geneva University Hospitals  
 Geneva, Switzerland

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## AN ADVERSE EVENT ASSOCIATED WITH HIP PROTECTORS

*To the Editor:* Hip protectors have been demonstrated to reduce fracture rates.<sup>1</sup> There are few descriptions of any adverse events associated with use of hip protectors. Of side effects described, most have been minor (e.g., not being comfortable (too tight/poor fit)).<sup>2</sup>

In January 2004, hip protectors were prescribed in a 74-year-old resident of an assisted living facility. One month later, she began to complain of right gluteal-area pain that radiated down her leg along the distribution of the sciatic nerve. The pain was worse after sitting for prolonged periods. Her history was noteworthy for mild Alzheimer's disease, treated depression, and hypothyroidism controlled with exogenous L-thyroxin. She got some relief of her pain from a Level 3 on the Functional Pain Scale to a Level 2 using acetaminophen and refecoxib.<sup>3</sup> Physical examination showed tenderness over the posterior superior iliac spine and an abnormal gait favoring her right leg. Tenderness was exacerbated in the seated position with external rotation of the leg and knee flexion. Within 6 weeks of discontinuing her hip protectors, the hip pain resolved completely.

Many clinicians have witnessed the delight of a patient who has had "wallet sciatica" resolve after simply discontinuing the practice of carrying a bulky billfold in the hip pocket. Other cases have been described of leg pain resolve after removal of piriformis muscle pressure.<sup>4</sup> This is believed to be the first case associating hip protectors with

piriformis syndrome or sciatica. Tight-fitting elastic or increased pressure from the protector pad over the piriformis muscle adjacent to the sciatic nerve is likely to be the source of compression on the sciatic nerve resulting in sciatic neuropathy and should be considered when similar complaints arise in individuals who have been prescribed hip protectors.

F. Michael Gloth III, MD, AGSF  
 Division of Geriatric Medicine and Gerontology  
 Johns Hopkins University School of Medicine  
 Baltimore, MD  
 Victory Springs Senior Health Associates  
 Reisterstown, MD

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## HOMICIDES OF DISABLED OLDER PERSONS BY THEIR CAREGIVERS IN JAPAN

*To the Editor:* Following the lead of the Netherlands and Germany, in April 2000 Japan launched a long-term care (LTC) insurance system nationwide in a courageous attempt to comprehensively solve the problems of caring for frail older people.<sup>1,2</sup> This new system was unprecedented in making the government rather than the family responsible for the care of the disabled elderly. Specifically, the goals of the LTC insurance system are to allocate limited resources to impaired elderly in a way that adequately reflects need, support home care, and reduce caregiver burden.<sup>3,4</sup> Under this care, the level of services provided are keyed to the degree of a recipient's impairment. To assess the effectiveness of the new insurance system, we investigated the prevalence of caregivers murdering frail older recipients because of exhaustion from the care burden before and after the inception of the insurance system in Japan. We employed the key words of "kaigo" (care) and "satsujin" (homicide) and collected more than 600 articles associated with caregiver murders between January 1997 and December 2003 using a computerized surveillance system (<http://www.asahi.com/>) provided by a major Japanese newspaper, the *Asahi Shinbun*. Thereafter, we carefully analyzed the eligibility of the articles to this study one by one and summed up the yearly cases accordingly. Eligible recipients were disabled persons who were aged 40 and older living with their caregivers in their own home and were killed by their caregivers because of exhaustion associated with the care burden (confirmed by police records). Cases were excluded if caregivers were drug abusers or had psychological disorders such as depression and schizophrenia.

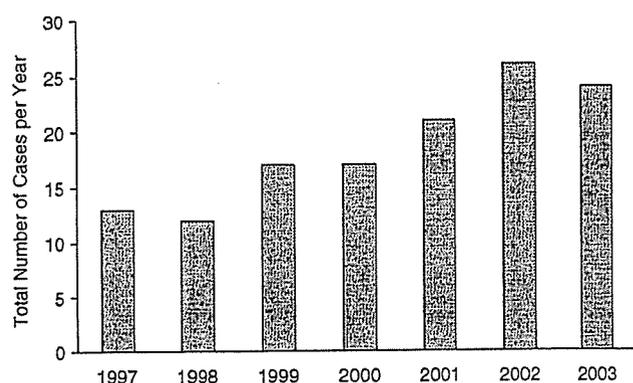


Figure 1. Annual prevalence of caregiver murders.

Finally, we found 130 cases eligible for this study. The mean age  $\pm$  standard deviation of the caregivers was  $66.3 \pm 13.4$  and that of the recipients was  $72.5 \pm 11.9$ . The most frequent cases were murder between sons or daughters and their parents (50%), followed by husbands and wives (47%) and others (3%). As shown in Figure 1, the annual prevalence of caregiver murder seems to be increasing even though the new LTC insurance was implemented in 2000. The recipients' principal physical conditions were dementia (57%), bedridden condition due to stroke with or without dementia (40%), and others (3%). The murders were by strangulation (68%), stabbing (13%), striking (9%), and other (10%). We could find no significant difference in any parameters described above before and after the new insurance system was begun.

We demonstrated that the current prevalence of murder by exhausted caregivers to the frail recipients was increasing rather decreasing after the inception of the new LTC insurance system. Now, 4 years after its inception, it seems necessary to ask whether the program has developed a fair and appropriate way of allocating limited resources to people with different diagnosis. Services are allocated based on the Government-Certified Disability Index.<sup>1,3</sup> Recent reports describe that the needs of demented elderly are often underestimated because of a lack of field-proven items to accurately assess their cognition and behavioral problems under the current insurance system.<sup>3,5</sup> This might be one explanation of the unexpected result of the present study, because most of the killed frail elderly suffered from dementia. The induction of Japan's new LTC system was quite significant in making clear the plight of the aged and their caregivers, but the system should be improved to lighten the caregiver's burden, especially in caring for demented people who require a great amount of assistance from family caregivers to live in the community.

Takashi Ohnui, MD

Mei He, MD

Naoki Tomita, MD

Hidetada Sasaki, MD

Department of Geriatric and Respiratory Medicine  
Tohoku University School of Medicine  
Sendai, Japan

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## TEACHING THE OLDER ADULT

*To the Editor:* Older adults learn in the same way as do all other adults.<sup>1</sup> They must be motivated and be in an environment that is conducive to learning (i.e., it must be quiet, well lit, at a comfortable temperature, and have a relaxed atmosphere).<sup>2</sup> The best motivator for adults is when they have an immediate need or requirement for the information. This is further enhanced when their personal goals and objectives are clarified and addressed before the information is presented. The older adult can benefit from certain adjustments to the teaching methodologies that address the various sensory impairments and cognitive changes common to this age group. (It is important to remember that not all older adults suffer from these.)

Visual deficits can be accommodated for by providing larger typeface (12 point or larger) and using a nonserif font with high contrast between type color and background. Auditory deficits are overcome by speaking distinctly and slowly, in a slightly louder voice, and at a deeper pitch than usual, while looking directly toward the person. The use of multiple-sensory input (i.e., written and auditory (also tactile and olfactory, if appropriate)) is helpful. Also, avoiding the necessity of writing or using small dials or buttons to access the information and eliminating background "noise" (auditory and visual) enhances accessibility of the information.<sup>3</sup>

Building upon previously acquired knowledge can accommodate cognitive changes, as can providing new information in shorter, simpler segments (no more than 3-5 points in one session). Use the same terms to refer to the same points each time, allowing the person to problem solve to come to conclusions on his/her own. Focus on problem solving and limit information to that necessary to make learning and retention easier. Frequent repetition of previously learned information (concepts) through different sensory channels and reducing the necessity of abstract thinking are also useful techniques to employ. Allow more time for older adults to absorb new information and permit them to set their own pace. Encouraging active participation and providing ways to reinforce memory can also improve learning and retention (e.g., posted lists/steps).<sup>3</sup>

Most older adults still prefer to learn in familiar ways: one-to-one oral instruction, written material, and classroom instruction—if it is relaxed and if they are treated with respect and dignity. However, the fastest-growing group of people learning to use the Internet is those aged 55 and older. This is likely to become a common method of learning for many older adults in the near future—within the next 10 years. It appeals especially because of its availability for those who may not be as mobile as they had been and because of its instant availability to fit into the increasingly busy lifestyle

mean ages at death of mothers of cases dead at younger than 75 versus those aged 90 and older were 70.4 and 70.9, respectively. No significant differences were found between the mothers' mean ages at death in relation to age at death in cases. The mean ages at death of fathers of cases dead at younger than 75 versus those aged 90 and older were 68.9 and 71.3, respectively. When comparing the extreme groups (cases dead at age 60–64 vs  $\geq 96$ ), a statistically significant association was found between fathers' lifespan and mean age at death of the cases (Table 1). This association remained when maternal and paternal lifespan were combined into one estimate. Thus, a trend for longevity was found in cases with fathers with longer lifespan. No association was found between mothers' and cases' lifespan. As described above, the current series was based on a birth-cohort from the end of the 19th century recruited from two small farming villages in northern Sweden judged to be homogenous with regard to living and working conditions and with limited effect of urban lifestyle. This study is, to our knowledge, the first published report addressing results that indicate different effect of mothers' and fathers' longevity with regard to cases' lifespan. The results in the current series indicate that the magnitude of paternal lifespan might have been stronger if the cohort had encompassed a larger proportion of very old cases ( $\geq 96$  at death), but despite this fact, there was a clear trend showing an association between fathers' and cases' lifespan.

In conclusion, fathers appear to be at least as important as mothers. Individuals reaching very old age (95) had older fathers. The finding that paternal (but not maternal) factors play a variable role upon age at death merits further examination.

Ola Landgren, MD, PhD  
Magnus Björkholm, MD, PhD  
Division of Hematology  
Fredrik Granath, PhD  
Anders Ekbom, MD, PhD  
Division of Clinical Epidemiology  
Department of Medicine  
Karolinska Hospital and Institutet  
Stockholm, Sweden

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## ACARBOSE ATTENUATES HYPOGLYCEMIA FROM DUMPING SYNDROME IN AN ELDERLY MAN WITH GASTRECTOMY

*To the Editor:* Dumping syndrome, a well-recognized complication of gastric surgery, is thought to result from the

rapid passage of carbohydrates into the small intestine, producing circulatory hypovolemia through an osmotic effect (early dumping) or a sharp rise in plasma glucose with subsequent hypoglycemia caused by an excessive insulin secretion (late dumping).<sup>1</sup> Sympathoadrenal activation, which is believed to act as a self-protective mechanism against an abrupt fall in plasma glucose,<sup>2</sup> is known to occur during late dumping, but no report has described the role of the sympathetic nervous system in the pathophysiology of late dumping syndrome. We present a case of sudden loss of consciousness associated with meals, which was diagnosed as late dumping syndrome and concomitant sympathetic nervous dysfunction and was successfully treated with an alpha-glucosidase inhibitor, acarbose.

A 78-year-old man was referred to our hospital for investigation of unexplained loss of consciousness in January 2004. He had a history of partial gastrectomy due to gastric cancer in 1996. He had been well until December 2003, when he had experienced sudden loss of consciousness without reactive vasomotor symptoms such as palpitation, sweating, or tremor approximately twice a week after a meal. After admission, brain, chest, and abdominal computed tomography scans and cardiovascular, electroencephalographic, hematological, and biochemical examinations were normal except for hyperglycemia (blood glucose  $> 250$  mg/dL) followed by hypoglycemia (blood glucose  $< 30$  mg/dL) after a meal. Late dumping syndrome was suspected, and an oral glucose tolerance test was performed. After glucose administration, the plasma glucose and insulin rose sharply from a basal value of 112 mg/dL and 2  $\mu$ U/mL to a peak level of 317 mg/dL and 215  $\mu$ U/mL at 60 minutes, respectively. At the second hour of the test, he developed a hypoglycemic coma with a blood glucose level of 28 mg/dL, whereas plasma norepinephrine level remained low ( $< 0.2$  ng/mL). He regained full recovery after glucose infusion. Other physical examinations revealed a positive head-up tilt test. Although there was no apparent structural heart disease, clear defects of diffuse myocardial meta-iodobenzylguanidine ((MIBG) an analog of norepinephrine) uptake were observed with iodide-123-MIBG single photon emission computed tomography (SPECT) imaging<sup>3</sup> (Figure 1). In contrast, thallium-201 SPECT distribution was normal.

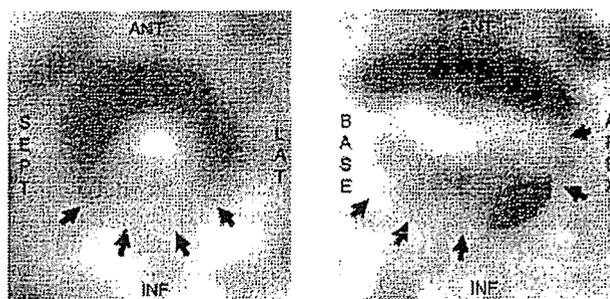


Figure 1. Clear defects of diffuse myocardial meta-iodobenzylguanidine (MIBG) uptake on iodide-123-MIBG single photon emission computed tomography (SPECT) imaging were observed (arrows). The left panel shows an axial view; the right panel shows an apical view of the left ventricle. ANT = anterior; LAT = lateral; INF = inferior; SEPT = septal.

A diagnosis of late dumping syndrome with idiopathic autonomic failure was made,<sup>4</sup> and the patient was referred for acarbose treatment.<sup>5</sup> Acarbose was orally administered at a dose of 100 mg, three times a day before each meal. Thereafter, the rapid changes of plasma glucose level associated with a meal were attenuated (range 100 mg/dL–200 mg/dL), and the patient was free from dumping-related loss of consciousness.

Acarbose attenuates the postprandial increase in plasma glucose levels and is widely used for the treatment of non-insulin dependent diabetes mellitus.<sup>6</sup> A previous report showed that acarbose attenuates postprandial reactive hypoglycemia and improves symptoms in patients with dumping syndrome.<sup>5</sup> The present case suggests that sympathetic nervous activation plays a preventive role against the development of severe late dumping and that acarbose is effective for the treatment of hypoglycemic coma associated with late dumping.

Mitsuhiro Yamada, MD  
Takashi Ohruji, MD  
Masanori Asada, MD  
Kota Ishizawa, MD  
Satoru Ebihara, MD  
Hiroyuki Arai, MD  
Hidetada Sasaki, MD

Department of Geriatric and Respiratory Medicine  
Tohoku University School of Medicine  
Sendai, Japan

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## OPTIMIZING ANTILIBIDINAL TREATMENT WITH MEDROXYPROGESTERONE ACETATE

*To the Editor:* Sexual disinhibition in demented patients is not a common problem<sup>1–3</sup> but can be a tremendously disruptive one for all concerned. Medroxyprogesterone acetate (MPA) has been shown to be effective for and well tolerated by such patients, generally in modest doses.<sup>3,4</sup> The mechanism of action seems to be suppression of follicle-stimulating hormone and luteinizing hormone secretion at the pituitary level, leading to decreased testosterone production and decreased libido.<sup>2</sup> Although there is some contrary evidence,<sup>5</sup> reduction in serum testosterone levels seems to correlate with behavioral improvement. We recently cared for a seemingly refractory patient in whom

monitoring of serum testosterone levels ultimately led to successful treatment with a fairly high dose of MPA.

A 76-year-old man with a 15-year history of alcoholic dementia had had ongoing problems with sexually disinhibited behavior for about 10 years. These behaviors included masturbating publicly and verbal and physical sexual advances toward women and had resulted in multiple hospitalizations and discharges from assisted living facilities. Medical history was noncontributory, and there was no evidence of hypersexual or paraphilic behavior or psychiatric illness (other than alcoholism) before the onset of the dementia. Mental status examination was significant for deficits in memory and executive function; there was no evidence of mania or psychosis.

The sexual behavior had failed to respond to various neuroleptics and mood stabilizers in the past but had remitted for 5 years with paroxetine, although ultimately the behavior recurred for unclear reasons and failed to respond significantly to substitution of intramuscular MPA in doses as high as 300 mg per week.

MPA was titrated as high as 600 mg per week, and paroxetine was ultimately reintroduced, but the sexual behavior did not improve significantly. At this point, a serum testosterone level of 72.1 ng/dL was noted. The MPA dosage was increased to 750 mg per week, and repeat testosterone level was 48.4 ng/dL. At that dosage, the sexual behavior improved markedly; there have been no further sexual advances toward women in the past 2 months, and he masturbates only rarely and discreetly in his room.

This patient responded to a much higher dose of MPA than other demented patients reported in the literature; Cooper<sup>3</sup> used a fixed dose of 300 mg weekly, and Weiner et al.<sup>4</sup> used doses of 100 mg to 200 mg every other week. We found that monitoring testosterone levels helped to explain the patient's apparent refractoriness and to guide successful treatment. This experience was similar to that of others; Cooper<sup>5</sup> reported a mean 90% reduction in serum testosterone levels in his successfully treated patients (we unfortunately did not check a pretreatment testosterone level in our patient), and Cordoba and Chapel<sup>6</sup> reported testosterone levels reduced "nearly to female values" (25 ng/dL–90 ng/dL,<sup>7</sup>) in their younger, nondemented patient. Serious sexual disinhibition is a potentially devastating problem in demented individuals, leading to hospitalization, restrictive placements, and potential legal liability; MPA can be effective in such patients, and monitoring of serum testosterone levels may be a useful strategy for optimizing treatment.

Jonathan T. Stewart, MD  
Department of Psychiatry  
College of Medicine  
University of South Florida  
Tampa, FL  
Geropsychiatry Section  
Bay Pines VA Medical Center  
Bay Pines, FL

## REFERENCES

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**Discussion.** Our patient improved with each course of IVMP, supporting the contention that GAD65 ataxia is an immune-mediated disorder. IVMP also reduced serum and CSF GAD65 antibody titers. In contrast, plasma exchange produced no immediate clinical benefit or reduction in CSF GAD65 antibody levels (although serum titers predictably decreased). These data suggest that CSF GAD65 antibody titers may correlate better with clinical response.

We also found an elevated CSF GAD65 specific index, indicative of intrathecal antibody production.<sup>9</sup> The association of elevated CSF GAD65 specific index and GAD65 antibody titers with disease severity suggests that intrathecal antibody production may be pathogenic. Moreover, the absence of cerebellar atrophy on MRI and marked clinical response to immunotherapy, with return of near-normal cerebellar function, argue against a destructive, cytotoxic process in our patient. A predominant humoral mechanism for GAD65 ataxia contrasts with that seen in paraneoplastic cerebellar degeneration in which CD8<sup>+</sup> cytotoxic T lymphocytes are likely pathogenic and autoantibodies are probably insufficient to cause disease.<sup>7</sup> If antibodies are primarily pathogenic, it remains unclear whether GAD65-specific or other antibodies are causative.

Our case is also notable because of the response to azathioprine, as evidenced by the patient's clinical remission. Azathioprine should be considered alongside IV corticosteroids in the management of GAD65 ataxia.

*From the Department of Neurology (N.R.M.F., I.S.L., T.M.B.), University of Virginia Health System, Charlottesville, and Smith Regional Internal Medicine (S.V.), Marion, VA.*

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## ACE activity in CSF of patients with mild cognitive impairment and Alzheimer disease

M. He, MD; T. Ohrai, MD; M. Maruyama, MD; N. Tomita, MD; K. Nakayama, MD; M. Higuchi, MD; K. Furukawa, MD; and H. Arai, MD

There is increasing evidence of angiotensin-converting enzyme (ACE) in the development of Alzheimer disease (AD).<sup>1,2</sup> However, little is known about the ACE activity in the CNS in living patients with AD. We therefore measured ACE activity in CSF in patients with mild cognitive impairment (MCI) and mild to moderate AD and compared the values with those of age-matched healthy control subjects. We also examined whether treatment with a brain-penetrating ACE inhibitor<sup>3</sup> can alter CSF ACE activity in patients with mild to moderate AD.

**Methods.** We registered 90 patients (mean age  $72.6 \pm 1.8$  [SE] years) who had undergone evaluations for memory disturbance at the Tohoku University Hospital Outpatient Clinic on Dementia in January 2003. Clinical assessments by geriatricians and neuropsychological examinations, including Mini-Mental State Examination (MMSE) and Wechsler Memory Scale-Revised, were performed for all subjects, as described previously.<sup>4</sup> Our established criteria<sup>4</sup> based on the current consensus<sup>5</sup> were used for a diagnosis of progressive MCI and AD-converted MCI. In detail, 28 individuals fulfilled the criteria for a diagnosis of amnesic MCI<sup>6</sup> at the time of the CSF examination. Fourteen of 28 patients (male/female ratio, 6:8) progressed over time. They lived independently during a 2-year follow-up and were considered as having progressive MCI.<sup>4</sup> Six of 28 subjects (male/female ratio, 3:3) showed clinical progression that warranted a diagnosis of dementia and ultimately met the National Institute for Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) diagnostic criteria for AD<sup>6</sup> and were categorized as having AD-converted MCI.<sup>4</sup> In the cur-

*Address correspondence and reprint requests to Dr. T.M. Burns, Neurology Department, University of Virginia Health System, PO Box 800394, Charlottesville, VA 22908; e-mail: tmb8r@virginia.edu*

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rent study, we enrolled both patients with progressive MCI and those with AD-converted MCI as the MCI group. A diagnosis of AD was made in accordance with the NINCDS-ADRDA criteria.<sup>6</sup> As a consequence, 20 patients (mean age  $72.9 \pm 1.2$  years, 9 men) fulfilled the diagnostic criteria for progressive MCI and AD-converted MCI (MCI group), 34 patients (mean age  $73.7 \pm 1.2$  years, 14 men) were diagnosed as having AD (AD group), and 20 subjects (mean age  $71.4 \pm 1.7$  years, 9 men) were found to be cognitively normal (normal group). Four (20%) of the 20 patients in the MCI group and 6 (18%) in the AD group received a 5-mg daily dose of donepezil hydrochloride at study entry.

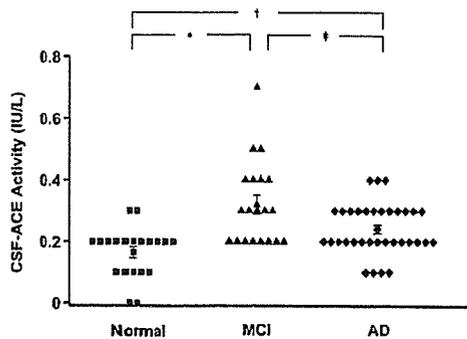
We collected CFS samples from each subject at baseline investigation. CSF samples were obtained by lumbar puncture before lunch between 1:00 PM and 2:00 PM in all subjects and were kept at  $-80^{\circ}\text{C}$ . ACE activity in the CSF was measured by the colorimetric method, which is based upon colorimetry of the quinoneimine dye produced from the substrate *p*-hydroxyhippuryl-L-histidyl-L-leucine by action of this enzyme, as described in detail previously.<sup>7</sup> CSF ACE assay was performed in duplicate in all samples. As there was no significant difference between the measurements, the mean value was adopted in the following analysis.

In 7 of 34 patients with AD who had hypertension, CSF was collected again after oral administration of a brain-penetrating ACE inhibitor, perindopril (2 mg/day)<sup>8</sup> for 1 month, and measurement of ACE activity in the CSF was repeated in these subjects. CSF collection was performed 5 hours after taking the last dose of perindopril in seven patients in the perindopril study. This study was approved by the Tohoku University Ethical Committee, and informed consent was obtained from participants and their caregivers before the study.

For group comparisons of clinical and biochemical variables, one-way analysis of variance (ANOVA) was done, followed by Tukey-Kramer multiple comparison test. Relationships between CSF ACE activity and MMSE scores were examined using a linear regression analysis. Correlations between two variables were tested by the *t* statistic. Significance was taken as  $p < 0.05$ .

**Results.** The mean baseline MMSE value was  $18.9 \pm 0.7$  (SE) in the AD group,  $25.0 \pm 0.4$  in the MCI group, and  $28.5 \pm 0.3$  in the normal group. CSF ACE activity was elevated in the MCI group ( $0.32$  [mean]  $\pm 0.03$  [SE] IU/L,  $n = 20$ ) vs the control group ( $0.17 \pm 0.02$  IU/L,  $n = 20$ ,  $p < 0.0001$ ). There was also an increase in the mean CSF ACE activity in the AD group ( $0.24 \pm 0.01$  IU/L,

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**Figure.** Individual CSF angiotensin-converting enzyme (ACE) activity (IU/L) in cognitively normal subjects ( $n = 20$ ) and patients with mild cognitive impairment (MCI;  $n = 20$ ) or Alzheimer disease (AD;  $n = 34$ ). A significant increase in CSF ACE activity was observed in patients with MCI (filled triangle) and AD (filled diamond) vs normal subjects (filled square). A difference in CSF ACE activity was also found between patients with MCI vs AD. \* $p < 0.0001$ , † $p = 0.0219$ , ‡ $p = 0.0170$ .

$n = 34$ ,  $p = 0.0219$ ) vs the control group (figure). Furthermore, CSF ACE activity in the MCI group was elevated vs the AD group ( $p = 0.0170$ ) (figure). There was no significant difference in the CSF ACE activity between the patients with and those without cholinesterase inhibitors. Elevated CSF ACE levels were significantly associated with lower baseline MMSE scores when normal subjects and patients with MCI were combined for analysis and also when normal subjects and patients with AD were combined for analysis. However, in all subjects, there was no significant correlation between CSF ACE levels and baseline MMSE scores (figure E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)).

The brain-penetrating ACE inhibitor perindopril inhibited CSF ACE activity in patients with AD after 1 month of treatment ( $0.24 \pm 0.02$  [before] vs  $0.13 \pm 0.03$  IU/L [after],  $n = 7$ ,  $p = 0.038$ ). The mean 1-year decline in MMSE scores during a 2-year follow-up in patients with AD treated with perindopril was lower vs patients with AD without perindopril treatment ( $-0.7$ /year in patients with perindopril vs  $-2.2$ /year in those without perindopril,  $p < 0.01$ ).

**Discussion.** In the current study, we have shown a substantial elevation in CSF ACE activity in patients with progressive and AD-converted MCI and mild to moderate AD as compared with age-matched healthy control subjects. MCI is a transitional state between the cognitive changes of normal aging and early AD.<sup>5</sup> A previous neuropathologic study described that ACE is overexpressed in the hippocampus, frontal cortex, and caudate nucleus in patients with AD.<sup>6</sup> The increased ACE activity in CSF in this study might reflect an increase in the brain regional ACE activity in MCI and AD, especially in MCI.

The role of ACE in the pathophysiology of AD remains controversial. Some researchers reported that ACE degrades amyloid  $\beta$ -protein in vitro, whereas others reported an ACE inhibitor has no effect on the degradation of amyloid  $\beta$ -protein in vivo.<sup>1,3</sup> There is also a possibility that increased CNS ACE activity might be involved in the cerebrovascular pathology in AD. It is reported that the enhanced formation of angiotensin II by increased ACE activity would result in an increased inhibitory effect of angiotensin II on acetylcholine release.<sup>2</sup> We have previously shown that brain-penetrating ACE inhibitors can reduce the incidence of AD in elderly hypertensive patients and also shown that a brain-penetrating ACE inhibitor inhibits the decline of cognitive function in patients with mild to moderate AD.<sup>3</sup> Furthermore, in this study, we showed that a brain-penetrating ACE inhibitor can significantly inhibit CSF ACE activity in patients with mild to moderate AD. We therefore assume that an increased CNS ACE activity might be involved in the progression of AD, although the precise mechanism remains unknown.

From the Departments of Geriatrics and Gerontology (M.H., T.O., N.T., K.N., H.A.) and Geriatric and Complementary Medicine (K.F., H.A.), Tohoku University School of Medicine, Sendai, and Brain Imaging Project (M.H., M.M.), National Institute of Radiological Sciences, Chiba, Japan.

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Address correspondence and reprint requests to Dr. T. Ohrai, Department of Geriatric Medicine, Tohoku University School of Medicine, Seiryō-machi, Aoba-ku, Sendai 980-8574, Japan; e-mail: [ohrai@geriat.med.tohoku.ac.jp](mailto:ohrai@geriat.med.tohoku.ac.jp)

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### VIDEO Action myoclonus–renal failure syndrome: A cause for worsening tremor in young adults

L. Vadlamudi, MBBS, FRACP, PhD;  
D.F. Vears, BBS/BSc(Hons); A. Hughes, MD FRACP;  
E. Pedagogus, MBBS, FRACP, PhD; and  
S.F. Berkovic, MD, FRACP

Action myoclonus–renal failure syndrome (AMRF) is an autosomal recessive disorder first described in 4 French Canadian pa-

tients, followed by a recent description of 15 cases from various countries.<sup>1,2</sup> The condition independently affects the kidney, with focal glomerulosclerosis causing renal failure and the brain causing progressive myoclonus epilepsy (PME) or progressive myoclonic ataxia (PMA).<sup>3,4</sup> Tremor is often an early feature. The diagnosis of tremor and myoclonus in patients with severe renal disease is challenging. Here we highlight the evolution of tremor in this syndrome in two new cases and emphasize problems in early diagnosis.

**Case reports.** **Case 1.** Case 1 is an Australian man of English ancestry with unrelated parents (figure). He was well until age 20 when end-stage renal failure developed, after a 3-month history of anorexia, nausea, and lethargy. Renal ultrasound demonstrated small kidneys; the etiology of renal failure was not established and renal biopsy not performed. He was treated with dialysis.

At age 22 he reported a mild, intermittent upper limb tremor occurring only with action and exacerbated by stress that had been present for 2.5 years. A very mild fine upper limb postural

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