LOW VITAMIN B_6 LEVELS ARE ASSOCIATED WITH WHITE MATTER LESIONS IN ALZHEIMER'S DISEASE

To the Editor: Vitamin B_6 is important in the reduction of a potentially toxic excess of homocysteine.[1] Low levels of vitamin B_6 are related to cognitive decline, but the underlying mechanism is not known. We hypothesized that vascular lesions in the brain may mediate this and studied the relation between vitamin B_6 levels and the presence of white matter lesions (WMLs) on magnetic resonance imaging (MRI) in patients with Alzheimer's disease (AD).

METHODS

One hundred twenty-three patients with AD who visited the outpatient memory clinic of the Alzheimer Center VU University Medical Center between 1997 and 2002 were included. All patients underwent a standardized examination that included blood tests, neuropsychological examination, and MRI. The standard MRI protocol included a coronal 3-mm T1-weighted and transverse 5-mm proton density or FLuid Attenuated Inversion Recovery (FLAIR) images on a 1.0 T scanner (Impact, Siemens AG, Erlangen, Germany) with an in-plane resolution of $1 \times 1\ mm^2$. Cortical atrophy was assessed as the mean of the maximum width of the left and right Sylvian fissure divided by the maximum brain width measured transpineally. Medial temporal lobe atrophy (MTA) was rated using a visual assessment of atrophy of the left and right medial temporal lobe separately. WMLs were rated semiquantitatively and were distinguished in the subcortical (number) and periventricular region (degree) separately.[2] The Mini-Mental State Examination (MMSE) was used as a measure of dementia severity. Plasma vitamin B_6 levels were determined using measurement of the active cofactor plasma pyridoxal-5-phosphate applying high-performance liquid chromatography using precolumn derivatization with semicarbazide and fluorescence detection. The overdispersed Poisson regression model was applied to investigate the relationship between the reciprocally transformed vitamin B_6 concentration and WMLs, adjusted for potential confounders.

Table 1. Characteristics of the Study Population (N = 123)

Characteristic	Value
Age, mean ± SD	69.3 ± 8.2
Male/female	59/64
Mini-Mental State Examination score, mean ± SD	20.5 ± 5.5
Plasma vitamin B_6, nmol/L, median (range)	33 (9–401)
Medial temporal lobe atrophy, mean ± SD	1.6 ± 0.1
Cortical atrophy, mean ± SD	0.1 ± 0.03
Periventricular WMLs, degree, median (range)	1 (0–9)
Subcortical WMLs, n, median (range)	8 (0–758)

SD = standard deviation; WMLs = white matter lesions.

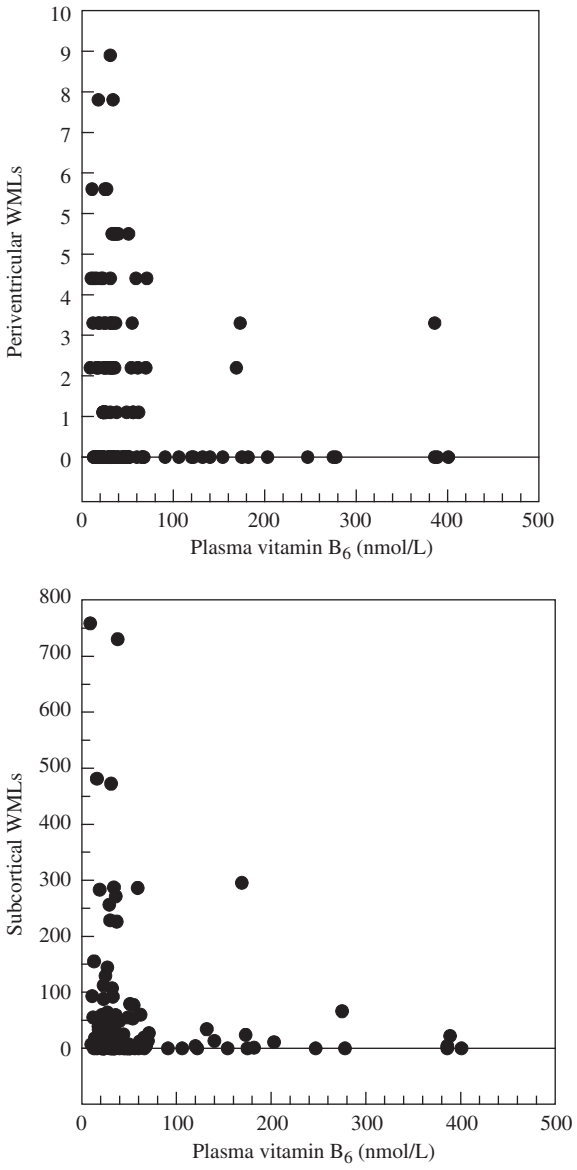

Figure 1. Scatter diagram depicting the association between periventricular white matter lesions (WMLs) (degree) and plasma vitamin B_6 concentrations (upper panel) and between subcortical WMLs (number) and plasma vitamin B_6 concentrations (lower panel).

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RESULTS

The plasma vitamin B_6 levels ranged from 9 nmol/L to 401 nmol/L. Sixty-three patients demonstrated any periventricular WMLs, and 88 patients any subcortical WMLs (Table 1). Poisson regression analysis showed that periventricular WMLs were dependent on the reciprocal of plasma vitamin B_6 (regression coefficient (B) = 9.22 ± 4.75, $P < .05$) as well as subcortical WMLs (B = 17.71 ± 6.69, $P < .01$), after adjusting for MMSE, MTA, cortical atrophy, and overdispersion, indicating that low B_6 levels were associated with higher WML load (Figure 1).

COMMENTS

We have demonstrated, for the first time, that there is a strong relationship between periventricular and subcortical WMLs and low vitamin B_6 levels in patients with AD. Low levels of B_6 could be the result of malnutrition as part of the already ongoing dementia process. We do not think that this influenced our findings because the patients were relatively mildly affected. Homocysteine, which is partially metabolized through the transsulfuration pathway, where homocysteine condenses with serine to cystathionine, a vitamin B_6–dependent reaction, may mediate the observed effect of B_6 on WMLs. Consequently, low vitamin B_6 levels may cause high homocysteine levels, thus promoting the proliferation of smooth muscle cells and initiating or accelerating the progression of atherosclerosis,[3] which is related to WMLs. There is conflicting evidence on the relationship between vitamin B_6 and vascular disease in dementia. A previous study[4] showed that low vitamin B_6 levels in patients with AD were not related to cardiovascular disease, whereas another study[5] showed that patients with subcortical vascular dementia had lower vitamin B_6 values. Both studies demonstrated a significant relationship between high homocysteine levels and vascular disease in their patients. The implication of the current findings is that low vitamin B_6 levels may increase the vascular burden in the brain of patients with AD. These results may provide a rationale for intervention studies examining the effect of vitamin B_6 supplementation on vascular changes in the brain in relation to the incidence and course of AD.

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HYPERIMMUNOGLOBULIN A AND CELIAC DISEASE IN THE ELDERLY

To the Editor: Celiac disease (CD) is a common disorder caused by abnormal immunological response to gluten proteins, leading to increased enterocyte apoptosis and villous atrophy.[1] CD is still widely perceived as a malabsorption syndrome of childhood, but the initial diagnosis is often made in adulthood and also in the elderly. Approximately 2% to 10% of CD is diagnosed in those aged 70 and older.[2] Older patients can present with nonspecific symptoms such as asthenia, anorexia, weight loss, fever, osteoporosis, dementia, and sero-negative polyarthritis.[3] Although diarrhea, steatorrhea, and weight loss are typical for patients with CD, they may be minimal or absent, often resulting in a delay in diagnosis. Most people with gluten sensitivity have latent CD, with such mild manifestations that a diagnosis is not made.

We report the case of a 74-year-old woman who presented in January 1997 with a 10-year history of mild abdominal pain attributed to diverticulosis of the colon. She had suffered from hyperthyroidism at age 36, hepatitis A at age 58, and type II diabetes mellitus diagnosed at the age of 67 and treated with a carbohydrate-restricted diet. On physical examination, no major abnormalities were found. Laboratory findings showed high serum concentration of immunoglobulin (Ig) A (1,420 mg/dL, n.v. 60–400 mg/dL); IgG and IgM were also elevated (1,580 mg/dL (normal value (n.v.) 600–1,450 mg/dL) and 703 mg/dL (n.v. 50–250 mg/dL), respectively). An erythrocyte sedimentation rate (ESR) of 108 mm/h was found, and circulating immune complexes were slightly elevated, with normal C3 and C4 levels. Hemoglobin was 13.2 g/dL; nuclear antibodies, mitochondrial antibodies, smooth muscle antibodies, liver-kidney-microsomal antibodies, carcinoembryonic antigen, α-fetoprotein, and carbohydratic antigen 19.9 were undetectable; and Bence-Jones protein was absent. Other routine analyses were normal. Bone densitometry demonstrated marked osteoporosis (bone mass density L2-L3 = 0.700).

Abdominal ultrasonography and computerized tomography did not indicate neoplastic disease.

At the end of 1997, the patient showed no substantial variations of the main laboratory findings. To evaluate the presence of myelodysplasia, a skeletal scintiscan with ^{99m}Tc-diphosphonates was performed, which was normal. The following diseases were considered as possibly associated with hyper-IgA: myeloma, monoclonal gammopathies of undetermined significance, Wiskott–Aldrich syndrome, ataxia telangiectasias, persistent neutropenia, alcoholic liver disease, initial phase of neoplastic disease, familial thrombocytopenia, meningitis, Berger's glomerulonephritis, Behçet's disease, Wegener's granulomatosis, Goodpasture's syndrome, psoriasis, and CD.

To test the hypothesis that elevated IgA level could be secondary to CD, the following investigation was performed: antigliadin antibodies IgA 55 UA/mL (n.v. < 20), antiendomysial antibodies (EMA) IgA 1:80 (n.v. < 1:5), and osteocalcin greater than 86 ng/mL (n.v. 3.1–13.7). Fiberoptic esophagogastroduodenoscopy and small-bowel biopsy showed total villous atrophy.

The patient was put on a gluten-free diet (GFD) with progressive normalization of IgA, IgG, IgM, EMA, ESR, and osteocalcin and a progressive increase in body weight and bone mass density (L2-L3 = 0.823). Her overall clinical conditions were satisfactory when last seen in May 2004.

In this patient, diagnosis of CD was made based on examinations aimed to explain the presence of elevated serum IgA levels. Hyper-IgA is described in a restricted minority of CD patients, although in this patient, it was the only feature indicating the diagnosis, because other symptoms/signs were masked by the coexistence of other gastrointestinal abnormalities (mild abdominal pain) or are common in elderly (osteoporosis). The diagnosis of CD and the introduction of a GFD resulted not only in Ig normalization, but also in significant osteoporosis improvement, as described in the literature for younger patients.[4] This fact deserves special consideration because the effect of osteoporosis on the elderly and prompts the importance of CD diagnosis and GFD introduction in older individuals. Moreover, a protective role of GFD against malignancy in CD, especially cancer of the mouth, pharynx, esophagus and lymphoma has been demonstrated.[5] Ig alterations, including IgA increase, can suggest the possibility of lymphomatous transformation arising as a complication of celiac enteropathy,[6] although the presence of enteropathy-associated T-cell lymphoma was excluded because the clinical course was not aggressive, the response to GFD was good, and there were no malignant T lymphocytes within the intestinal inflammatory-cell infiltrate.

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A WARM BATH

To the Editor: I very much enjoyed reading the two articles[1,2] and the editorial[3] on the vexing subject of bathing demented patients. This material helps us to understand how to cope with this difficult issue, although your readers might be interested to learn that this problem, in one form or another, has been around for quite a while. For example, in an attempt to provide more humane care for psychiatric patients in general, and those with dementia in particular, in 1891, the influential German psychiatrist, Emil Kraepelin, supported what was then called "duration bathing."

Following his lead, Alois Alzheimer introduced this therapy together with his superior, Professor Emil Sioli, at the Frankfurt Asylum for the Insane and Epileptic. It has even been documented that Alzheimer's first patient, "Auguste D.," was treated with such bath therapy.[4] In 1892, at the Karlsruhe Conference of Southwest German Psychiatrists, the then-28-year-old Alzheimer spoke about how he and Sioli had attempted to improve the conditions of their charges in the "restless patient units." As described in his biography,[4] "Alzheimer had told how he, together with . . . [the] director, Prof Sioli, soon introduced the bathing treatment, 'with which conditions changed abruptly. The introduction of permanent bathing proved to be an uncommonly beneficial practice.'"

Just the year before, Kraepelin had lectured, also in Karlsruhe, on his positive view of duration bathing and offered specific recommendations with respect to baths, "The water temperature . . . [should be] continually monitored by personnel and regulated as much as possible according to the comfort of the patients through the addition of warm or cold water; it fluctuates a little around 34° Centigrade." In comparison with the usual situation of the day, under which, as Alzheimer explained, psychotic patients were usually roughly treated, he and Sioli found that, with bath therapy, "all means of coercion still in use, such as tight gloves, indestructible suits, and, above all, isolation, are made almost completely unnecessary."

Not surprisingly, not all physicians of the day accepted these recommendations, and Kraepelin later remarked in his memoirs that "to his astonishment, [my] duration bath therapy initially encountered intense resistance. However, it was supported by several other psychiatrists, particularly by Alzheimer." Water therapy, related to the earlier European spa movement and the later development of hydrotherapy,[5] also crossed the Atlantic and was used by many American physicians, albeit in a less kind and gentle way. Perhaps in

keeping with the harsher American climate and influence of the Protestant ethic, cold-water wraps were the rule in the New World.

Almost 100 years after Alzheimer's death, we seem to have come full circle in our attempts to address humanely with the behavioral manifestations of dementia. Clearly, one hopes that articles such as these will prevent us from throwing out this important form of treatment along with the bath water.

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EFFECTS OF PHYSICAL EXERCISE ON PLASMA CONCENTRATIONS OF SEX HORMONES IN ELDERLY WOMEN WITH DEMENTIA

To the Editor: Physical exercise may slow the functional decline in elderly people and has been associated with a low incidence of dementia.[1] Physical activities have shown favorable effects on cognitive function as well as on neuropsychiatric symptoms and behavioral disturbance in demented subjects,[1,2] the mechanism of which is currently unknown. Because low plasma levels of sex hormones have been implicated in dementia,[3] it is reasonable to hypothesize that physical exercise could elevate plasma sex hormone levels. Here, we report a preliminary study in which daily physical exercise for 3 months increased the plasma levels of sex hormones, including dehydroepiandrosterone (DHEA) and testosterone, in elderly women with dementia. Thirteen women (aged 74–91, mean age ± standard deviation 84 ± 5) living in group homes for the elderly (small-scale facilities providing communal living) located in Nagano Prefecture, Japan, were enrolled. They were diagnosed as having Alzheimer's disease according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, but did not have malnutrition, malignancy, or endocrine disease. Blood sampling and functional assessment were performed at baseline, at the end of a 3-month exercise program, and at the end of a 3-month follow-up period, during which the subjects returned to ordinary sedentary living. The exercise program consisted of stretching and mild resistance training using a chair and a 0.5-kg weight. The exercise was performed as a group, with training for 30 minutes daily under the instruction of a physical therapist twice a week and by other caregiver staff five times a week. Care other than exercise was comparable throughout the study. Fasting blood samples were collected early in the morning before exercise. A commercial laboratory determined plasma levels of estradiol, testosterone, DHEA, DHEA sulfate, and sex hormone–binding globulin, in addition to blood cell counts and blood chemical parameters. Basic activities of daily living (ADLs) were assessed using the Barthel Index and cognitive function using the Mini-Mental State Examination.

At baseline, the subjects showed moderate cognitive impairment and dependency and relatively low sex hormone levels (Table 1). After 3 months of exercise, significant increases were found in plasma levels of testosterone of 18%, estradiol of 38%, and DHEA of 37%, all of which returned to the baseline levels 3 months after cessation of the exercise program. A similar alteration was found in plasma DHEA sulfate level, but the increase by exercise was not statistically significant (mean ± standard error 452 ± 62 ng/mL at baseline, 508 ± 72 ng/mL after exercise, and 464 ± 77 ng/mL after discontinuation). Sex hormone–binding globulin, albumin, and other blood parameters did not change throughout the study (Table 1 and data not shown). Despite the increases in sex hormones after the exercise program, neither Barthel Index nor Mini-Mental State Examination scores changed significantly during the study.

Table 1. Effects of Daily Physical Exercise on Plasma Concentrations of Sex Hormones in Elderly Women with Dementia (N = 13)

Measurement	Baseline	Exercise (3 Months)	Discontinuation (3 Months)
	Mean ± Standard Error of the Mean		
Testosterone, ng/dL	51.4 ± 3.3	60.8 ± 3.3†	47.9 ± 3.9
Estradiol, pg/mL	15.2 ± 1.2	21.0 ± 1.2†	19.4 ± 2.9
Dehydroepiandrosterone, ng/mL	1.84 ± 0.29	2.52 ± 0.41*	1.95 ± 0.27
Sex hormone–binding globulin, nmol/L	75.0 ± 6.1	69.1 ± 8.1	68.3 ± 8.3
Barthel Index	75.0 ± 5.4	70.0 ± 7.1	66.5 ± 9.4
Mini-Mental State Examination score	13.9 ± 1.9	13.8 ± 2.0	12.4 ± 2.5

$P <$ *.05; †.01 versus baseline using paired *t* test.

Previous studies[4,5] have shown stimulatory effects of endurance or resistance exercise on circulating hormones in healthy postmenopausal women; metabolic alterations and increased blood flow of endocrine organs via nitric oxide and cyclic adenosine monophosphate production may play a causal role, but hormonal responses in frail or demented women have not been examined. In the present study, plasma levels of estradiol, testosterone, and DHEA were higher after 3 months of physical exercise in elderly women with dementia, whereas cognitive function and basic ADLs did not improve. Given the protective effect of exercise and sex hormones on cognitive impairment, a control sedentary group should be included to examine whether this exercise program might delay cognitive decline. Nevertheless, the finding that exercise can increase plasma sex hormone levels in demented women provides a mechanistic insight into the effect of exercise or physical activities on cognitive impairment. The results of this preliminary study need to be confirmed using larger randomized, controlled trials with longer follow-up periods.

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RACIAL DIFFERENCES IN PRESSURE ULCER PREVALENCE IN NURSING HOMES

To the Editor: We read with great interest the recent article regarding black/white differences in the rate of nursing home–acquired pressure ulcers. Indeed, the findings reported were similar to what was found using the Health Care Financing Administration's Multi-State, Case-Mix and Quality Demonstration Project, which involved all Medicare/Medicaid certified nursing homes (n = 1,492) in five U.S. states (Kansas, Maine, Mississippi, New York, South Dakota). We identified 223,448 entrants to nursing homes in these five states over a 4-year period (1992–96). Patients were evaluated using the federally mandated Resident Assessment Instrument, which includes a 300-item Minimum Data Set (MDS). At least 100 residents of each racial/ethnic category were required. A nested linear model provided estimates of state- and sex-stratified differences in pressure ulcer prevalence after adjustment for pressure ulcer risk factors. Across all state/sex strata, blacks were substantially less likely than whites to have a Grade I pressure ulcer recorded. Higher-grade ulcers (II–IV) were, alternatively, consistently higher in blacks than whites, and even greater disparities were seen when only the highest-grade (IV) ulcers were compared. These findings were slightly adjusted when physical mobility (as measured by activities of daily living) was controlled for, although not so much as to change the basic interpretation. Control by additional clinical, diagnostic, behavioral, social, facility, and area-level characteristics failed to reveal any further confounding, demonstrating that this analysis was robust to adjustment for a wide-ranging set of factors identified or hypothesized as risk factors for pressure ulcer development. Moreover, it also observed that pressure ulcer prevalence in Native Americans demonstrated a similar pattern in South Dakota and Mississippi to that of whites; rates of Grade I ulcers were generally lower, whereas higher-grade ulcers were more common in Native Americans than in non-Hispanic whites.

Underdiagnosis of low-grade pressure ulcers in racial minorities, with subsequent progression to open lesions of higher grade, is largely consistent with these findings, as well as the findings of another study.[1] It has been long noted that the definition of low-grade pressure ulcers (persistent nonblanchable erythema) could result in the underdiagnosis of these lesions on dark skin. Because detection of low-grade pressure ulcers is an important factor in preventing their progression to higher stages, underdiagnosis likely contributes to the higher rates of high-grade ulcers found in older blacks and Hispanics. The relationship between contextual factors (such as resources and staffing) related to the types of nursing homes serving predominantly people of color and the underdiagnosis of pressure ulcers needs to be explored. Facilities serving primarily African Americans may have fewer funds and consequently offer fewer services and provide less staff training and amenities than other facilities.[2,3]

Although attempts have been made to enhance the detection of low-grade ulcers in blacks and Hispanics,[4] the extent to which public reporting of quality indicators focused on pressure ulcers and other quality improvement initiatives[5] is likely to reduce or exacerbate[3] racial/ethnic differences in pressure ulcer occurrence in nursing homes remain to be evaluated.

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NON-SMALL-CELL LUNG CANCER PATIENTS UNSUITABLE FOR FIRST-LINE CHEMOTHERAPY: A NEW CATEGORY OF PATIENTS FOR CLINICAL STUDIES?

To the Editor: Gefitinib (Iressa, ZD1839, AstraZeneca UK Limited, Macclesfield, Cheshire, UK) is a novel, epidermal growth factor receptor tyrosine kinase inhibitor approved in many countries for advanced non-small-cell lung cancer (NSCLC). Within an expanded access program (EAP), 14 patients aged 70 and older with NSCLC were treated with oral gefitinib (250 mg/d) as first-line treatment because of a medical contraindication to chemotherapy. One patient had a long-lasting objective response (>11 months), and seven patients experienced disease stabilization (median duration 6 months). Gefitinib was generally well tolerated. These results indicate that patients with NSCLC who are unable to receive chemotherapy can benefit from first-line treatment with gefitinib and should be further investigated in well-designed clinical trials.

Single-agent chemotherapy prolongs the survival of elderly and unfit patients with advanced NSCLC and improves overall health status and quality of life, although this benefit is achieved at the cost of some drug-related toxicity.[1,2] Many aspects of the treatment of unfit NSCLC patients are still to be optimized, including therapeutic alternatives for patients excluded from standard approaches because of multiple comorbidities, which are common in the elderly.

Table 1. Baseline Characteristics and Reasons for Exclusion from Chemotherapy (N = 14)

Patient	Age	Eastern Cooperative Oncology Group PS	Disease Stage	Disease Status Before Gefitinib Treatment	Cause of Exclusion from Chemotherapy
1	73	1	II	PD	Ischemic cardiomyopathy with right ventricular ejection 30%; atrioventricular conduction block III; diabetes mellitus type II, severe bronchopneumopathy
2	75	1	IV	PD	Moderate bronchopneumopathy, megacolon, diabetes mellitus type II, vasculopathy
3	77	0	IV	PD	Mild bronchopneumopathy, ischemic cardiomyopathy (previous cardiac infarction), serum creatinine 1.98 mg/dL, aortic aneurism (4 cm)
4	74	2	IIIB	FD	Bronchopneumopathy, ischemic cardiomyopathy (previous bypass), PS 2
5	76	2	IIIB	FD	Hypertension, PS 2 due to moderate dyspnea, previous laryngectomy
6	79	1	IIIB	PD	Ischemic cardiomyopathy with arrhythmia, moderate hypertension, diabetes mellitus type II, severe bronchopneumopathy
7	72	1	IV	FD	Diabetes mellitus type II, atrial fibrillation, episode of respiratory failure during surgery (aortic stenosis) 2 months previously
8	73	1	IV	FD	Alcoholic liver cirrhosis with thrombocytopenia 82 $\times$ 10^3/mm (transaminase $<$ 2 $\times$ normal, normal bilirubin), moderate aortic stenosis
9	75	2	IV	FD	PS 2 due to moderate dyspnea with cough, severe depression syndrome
10	80	2	IV	FD	Postinfarct cardiomyopathy (ventricular ejection fraction 30%), PS 2, serum creatinine 1.68 mg/dL
11	82	1	IV	FD	Severe bronchopneumopathy, advanced age
12	72	2	IIIB	FD	Ischemic cardiomyopathy with unstable angina, moderate hypertension, and bronchopneumopathy
13	72	1	IV	PD	Ischemic cardiomyopathy, hypertension, weakness in right side of body after intracranial hemorrhage (5 years previously)
14	74	2	IV	FD	Severe bronchopneumopathy, previous ischemic stroke, PS 2 due to pain, aortic aneurism

PS = performance status; PD = progressive disease; FD = first diagnosis.

Table 2. Response and Survival for Patients Who Had Not Received Prior Chemotherapy

Patient	Response	Response Duration (Months)	Survival (Months)
1	SD	2	4
2	SD	6	7
3	SD	15+	15+
4	PD	—	3
5	SD	11+	11+
6	PD	—	2
7	SD	2	4
8	SD	6	7
9	PD	—	1
10	PD	—	1
11	PD	—	3
12	PD	—	2
13	PR	11+	11+
14	SD	6	8

SD = stable disease; PD = progressive disease; PR = partial remission.

Phase I and II studies have demonstrated that gefitinib, an orally active epidermal growth factor receptor tyrosine kinase inhibitor,[3] is well tolerated and provided clinical benefit (tumor regression and stable disease, associated with symptom relief) in more than 40% of symptomatic patients with advanced pretreated NSCLC.[4,5] In February 2001, as part of an EAP, gefitinib (250 mg/dy) was administered to patients with advanced NSCLC. According to the EAP criteria, to administer gefitinib as first-line treatment, the investigator had to be of the opinion that the patient was not medically suitable for chemotherapy. Each patient was also required to have a performance status of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale and adequate hematological, renal, and hepatic parameters. All patients provided written, informed consent. Patients were evaluated every 4 to 6 weeks with regard to response according to Response Evaluation Criteria in Solid Tumors and toxicity according to National Cancer Institute common toxicity criteria (version 2.0).

Consistent with these criteria, 14 of the 39 patients aged 70 and older who were treated from February 2001 received gefitinib as first-line treatment because of a medical contraindication to chemotherapy. Most of these patients were male (n = 12) and had an ECOG performance status of less than 2 (n = 8). The median age was 74.5 (range 72–82). Six patients had adenocarcinomas. Other histological subtypes included squamous cell carcinoma (n = 2) and poorly differentiated carcinoma (n = 6). When gefitinib treatment was started, five patients had had disease progression during recent months. These patients had been diagnosed many months earlier but had not received medical treatment. The remaining patients' NSCLC had been diagnosed a few days before starting treatment. Three patients had previously received palliative radiotherapy. The baseline patient characteristics and the comorbidities that excluded these patients from chemotherapy are shown in Table 1.

Seven patients experienced disease stabilization, with a median duration of 6 months (range 2–15 months). One long-lasting objective response was observed (>11 months). Table 2 shows the duration of disease stabilization and partial remission and survival time for each patient. Median and 1-year survival for the series were 4 months (range 2–15 months) and 21.4%, respectively.

The most common adverse drug reactions were Grade 1/2 skin rash and diarrhea (n = 3 and n = 5, respectively). One patient experienced Grade 3 skin rash. Treatment was interrupted for 2 weeks in two patients (Grade 3 skin rash, n = 1, and Grade 1 elevated transaminases, n = 1); both restarted therapy at the full dose (250 mg/d). One patient received gefitinib every other day because of mild nervous excitement. Hematological toxicity and drug-related interstitial lung disease were not observed. Eleven patients received gefitinib until disease progression, and three patients are still receiving treatment.

Through the gefitinib EAP, this patient series has identified a new category of patients suitable for antitumor treatment. The better therapeutic index of gefitinib than of single-agent chemotherapy enabled these patients to receive treatment. Gefitinib provided disease stabilization in half of the patients and one long-lasting partial remission. Moreover, gefitinib was generally well tolerated and, in particular, did not seem to worsen comorbidities. Despite the limited size of this series, it demonstrates that some patients excluded from chemotherapy because of multiple impaired organ function or comorbidities, with no other treatment choice but best supportive care, benefited from treatment with gefitinib. This complex category of NSCLC geriatric patients should be studied further in well-designed, multidisciplinary clinical trials.

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TREATMENT OF VALPROATE-INDUCED HYPERAMMONEMIA

To the Editor: Hyperammonemia is a fairly common complication of valproic acid therapy.[1–3] Although asymptomatic in most patients,[1–3] hyperammonemia may sometimes be associated with lethargy, delirium, and coma.[4,5] Aside from recommendations to dechallenge valproate in such cases, little has been written about treatment.

A 79-year-old man with a lifelong history of paranoid schizophrenia was admitted because of combative behavior in a nursing home. Medical history was significant for a well-controlled seizure disorder, coronary artery disease, and benign prostatic hypertrophy. There was no evidence of dementia and no alcohol consumption for at least 10 years. Medications included olanzapine 15 mg at bedtime, phenytoin, amlodipine, finasteride, risedronate, and aspirin.

Olanzapine was continued, and valproic acid was added on admission. He initially did well, and valproate dosage was soon increased to 750 mg three times a day, attaining a serum level of 48.5 mg/mL. Within 2 days, the patient became lethargic, confused, and disoriented. There was no asterixis or evidence of intercurrent illness or covert seizure, free and total phenytoin levels remained therapeutic, and liver enzymes were within normal limits. Serum ammonia level was 89 mmol/L; free and total carnitine levels were within normal limits.

Valproate was discontinued, and the patient was treated with intravenous hydration, 60 g protein restriction, and lactulose 45 ml every 4 hours. His response was rapid and complete; after 2 days he was alert and oriented, and his serum ammonia level was normalized. He was ultimately discharged on olanzapine monotherapy and has done well for the past 6 months.

To our knowledge, this is the first report of treatment of valproate-induced hyperammonemia with lactulose. A previous study reported the use of lactulose in a 9-year-old boy with Down's syndrome,[6] but the patient developed chronic hyperammonemia persisting 2 years after discontinuation of valproate. The mechanism by which valproate induces hyperammonemia is unclear but is believed to be related to inhibition of the urea cycle enzyme carbamyl phosphatase and resultant inability to incorporate ammonia into urea.[3,5]

Factors predictive of symptomatic versus asymptomatic hyperammonemia have yet to be elucidated; our patient had a therapeutic valproate level and normal liver enzymes, which is consistent with others' experience.[3–5] The differential diagnosis of lethargy or confusion in a psychiatric population is broad, and hyperammonemia is a treatable cause that should be considered in patients receiving valproic acid.

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FUNCTIONAL ASSESSMENT AND INFECTIOUS DISEASES

To the Editor: We read with interest the paper by Torres et al.[1] on the importance of functional assessment as a predictor of outcome in the elderly with infectious diseases and the related editorial by High.[2]

We agree on the relevance of measuring function to "accurately model mortality risk in seniors," but we think that a broader approach is needed,[3] i.e., the clinical and biological mechanisms mediating the interaction of an acute disease such as pneumonia with the loss of function and their effect on mortality should be clarified.

The focus is High's statement, "functional status measures assess something different from age, comorbidity, and even frailty." We propose that a loss of functional status mirrors a condition of frailty sensitive to negative health events (e.g., pneumonia) and is at the same time an independent predictor of outcome (mortality).

We present data obtained from a population of 1,493 elderly patients consecutively admitted to the Acute Care for the Elderly Medical Unit (ACE-MU) in Brescia, Italy, during a 12-month period. Admission to the ACE-MU is mainly (82%) through the emergency department.

A trained staff of geriatricians conducted a multidimensional evaluation, including information on demographics (age, sex, education, living site, living conditions, and caregiver or formal support availability), mental status, physical health, functional abilities, and social support was performed on the first day after admission using a standard protocol. Cognitive status was evaluated using the Mini-Mental State Examination;[4] self-reported disability was assessed using the Barthel Index[5] and the Lawton-Brody instrumental activity of daily living scale.[6]

Somatic health was evaluated using the detection of single symptomatic diseases uncontrolled by therapy, whereas comorbidity was computed using the Charlson Index.[7] Severity of pneumonia was measured according to Acute Physiology And Chronic Health Evaluation (APACHE) II score and its Acute Physiology Score (APACHE II–APS).[8] Number of currently administered drugs was also recorded.

Pneumonia was diagnosed according to clinical signs and chest radiography and treatment provided according to

Table 1. Characteristics of 110 Patients Admitted to an Acute Care for the Elderly Medical Unit with a Diagnosis of Pneumonia According to Change of Functional Status (Five or More Points Loss at Barthel Index) Due to the Disease

Characteristic	Without Functional Change (n = 49)	With Functional Change (n = 61)	*P*-value*
Age, mean ± SD	80.2 ± 6.8	82.3 ± 6.8	.11
Female, n (%)	26 (53.1)	39 (63.9)	.33
Mini-Mental State Examination score at discharge, mean ± SD	21.9 ± 7.3	18.9 ± 9.2	.06
Barthel Index, mean ± SD			
Two weeks before hospitalization	80.6 ± 24.0	72.5 ± 25.8	.09
At admission	80.7 ± 24.0	36.4 ± 29.7	.00
At discharge	79.7 ± 26.5	43.4 ± 33.9	.00
Number of Instrumental Activities of Daily Living lost 2 weeks before hospitalization, mean ± SD	3.3 ± 2.8	5.1 ± 2.5	.004
Charlson Comorbidity Index, mean ± SD	7.5 ± 2.2	5.1 ± 2.6	.005
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	13.1 ± 3.2	16.7 ± 6.7	.00
Physiology score, mean ± SD	2.7 ± 2.7	5.5 ± 5.1	.00
Serum albumin, g/dL, mean ± SD	3.7 ± 0.7	3.4 ± 0.6	.009
Serum cholesterol, mg/dL, mean ± SD	183.1 ± 44.3	158.6 ± 46.7	.02
Hemoglobin, g/dL, mean ± SD	12.3 ± 2.2	11.2 ± 2.4	.06
Number of drugs, mean ± SD	3.6 ± 1.7	4.8 ± 2.5	.005
Length of stay, mean ± SD	7.6 ± 2.8	8.9 ± 4.7	.09
Six-month mortality, n (%)	5 (10.2)	22 (36.1)	.002

*Chi-square test for comparing frequencies and Student *t* test for comparing means.
SD = standard deviation.

the American Thoracic Society guidelines.[9] Six-month mortality was the outcome measure of the analysis.

Patients in whom functional change could not be assessed as a consequence of floor effect (i.e., those with a premorbid Barthel Index ≤ 10) were not included in this study.

Patients admitted for pneumonia (n = 110) were divided based on impairment of their functional status assessed using the difference between Barthel Index score 15 days before and on admission. It was found that the group of patients without changes in functional status (i.e., with a maximum loss of 5 points on the Barthel Index) were healthier according to various clinical and biological parameters and had a 6-month mortality of 10%, whereas patients with functional decline due to acute infectious disease (mean loss of 36 ± 27 points on the Barthel Index) were in worse clinical condition and had 36% mortality in the same period. Moreover, after adjustment for factors associated with mortality in bivariate analysis (aged ≥ 80, being male, pneumonia, cancer, anemia, congestive heart failure, cor pulmonale, chronic obstructive pulmonary disease, stroke, diabetes mellitus, liver diseases, dementia, depression, Charlson Index of ≥ 4, disability, APACHE II–APS subscore of ≥ 4, serum creatinine > 3 mg/dL, and serum albumin < 3.5 g/dL), change in functional status due to acute disease (relative risk (RR) = 2.1, 95% confidence interval (CI) = 1.2–3.5) but not pneumonia (RR = 0.5, 95% CI = 0.21–1.5) had an independent association with 6-month mortality.

These data indicate that pneumonia may affect different populations of older people differently: those with good premorbid health status whose function the disease affects only slightly, resulting in low short-term mortality, and those who are more sensitive to the effects of acute disease and have a high mortality rate.

May the latter group be defined as frail? In addition to definitions, it is important to stress the biological and clinical characteristics of the disease-disability relationship in infectious-disease research. On this matter it is time "to start preaching to the congregation and to the choir," that is, to involve geriatricians and nongeriatricians in considering the complex biological and clinical events acting as risk factors in old patients affected by pneumonia.

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AN ELDERLY MAN WITH MULTIPLE HEPATIC LESIONS: OTHER CONCEPTS ON AMEBIC LIVER ABSCESS

To the Editor: A classical description of amebic liver abscess (ALA) appears in the medical literature,[1–3] usually ignoring the other existing uncommon presentations.[4] A case of ALA diagnosed in an immunocompetent elderly adult with no alcohol intake and living in a nonendemic area is reported.

A 69-year-old man was admitted with a 1-week history of fever, chills, and abdominal pain. He denied significant alcohol consumption. His medical history was unremarkable. On admission, the patient was alert and in no distress. His pulse was 116 beats/min, his temperature was 38.8°C, and his abdomen was diffusely tender, more so over the right upper quadrant. Laboratory data showed white blood cell count of 16.4×10^9/L (8% bands, 80% neutrophils), serum aspartate aminotransferase 148 IU/dL, serum alanine aminotransferase 140 IU/dL, total bilirubin 1.5 mg/dL, and alkaline phosphatase 84 IU/dL. Serology to *Brucella* spp. *Salmonella* spp., hepatitis B and C, blood cultures (3/3), and microscopic stool examination for parasites and culture were negative. Ultrasound and computed tomography (CT) scan of the abdomen revealed multiple hypoechoic-hypodense lesions in the hepatic right lobe with a diameter of 2 to 6 cm (Figure 1). A CT-guided percutaneous catheter drainage of abscess was performed. Culture of aspirate was negative. An intravenous treatment with broad-spectrum antimicrobials including metronidazole was initiated. The antiamebic immunoglobulin G titer was 1:1,024 (0–64) using indirect fluorescent antibody test.

Human immunodeficiency virus (HIV) serology was negative. The patient was heterosexual. He had been born and was living in Guipúzcoa, a nonendemic amebic area in northern Spain. He had not traveled to any endemic country or had contact with individuals from endemic areas. He was discharged in a satisfactory state of health. Paromomycin was administered for 7 days.

ALA is most commonly seen in patients aged 20 to 40 with a history of traveling to or emigration from an endemic country.[1–4] Clinical presentation, laboratory data, and imaging findings were nonspecific in this patient, but his residence in a nonendemic area, absence of any epidemiological risk factors (immigration from a developing country, travel to the tropics, contact with individuals from endemic areas, residence in a psychiatric or nursing institution, homosexuality or bisexuality, immunosuppression (tuberculosis, HIV infection), history of alcohol abuse).[3,4] presentation as multiple abscesses, and his age of 50 and older led to an initial diagnosis of pyogenic liver abscess.[2,5] The differential diagnosis of ALA is extensive, including pyogenic disease (gallbladder, biliary tract, or liver), acute appendicitis, echinococcal cyst, perforation viscus, necrotic hepatoma, and other intra-abdominal infections, so the diagnosis of ALA is usually difficult, and a great amount of suspicion is required. A subset of 16 patients with ALA with no history of exposure has been described in whom severe immunosuppression such as tuberculosis or HIV infection was observed in up to two-thirds.[4] The absence of known risk factors for ALA in this patient suggest that aging may be a susceptibility factor in the development of ALA in some patients. Unusual presentations of ALA are frequently overlooked in literature[1–3] and so are not well known in medical practice, but these rare variants in the developed world[4,6] have clinical significance because they demand a high degree of suspicion to obtain a correct diagnosis and start an early appropriate treatment.

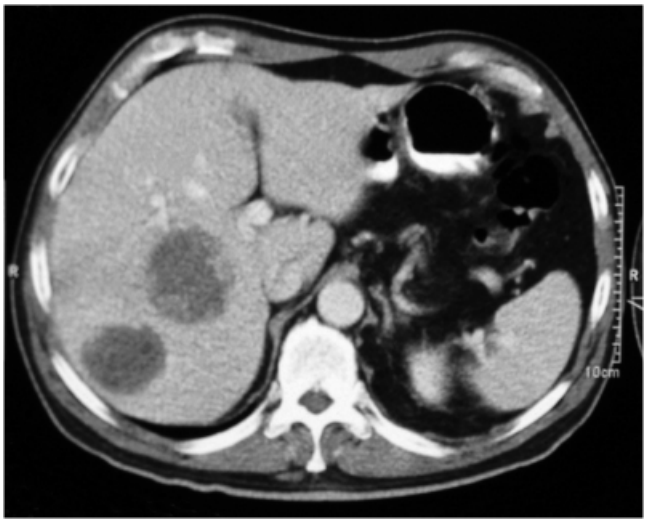

Figure 1. Computed tomography scan of the abdomen shows two large hepatic abscesses.

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PSEUDODIARRHEA CAUSED BY VAGINAL PESSARY IN AN ELDERLY PATIENT

To the Editor: Diarrhea and fecal incontinence are common complaints in the geriatric population and are often challenging to evaluate and manage. We report here an obscure cause of diarrhea in an older woman that may be more common than realized and easily missed by physicians.

Case Report

An independent 94-year-old woman with a history of hypothyroidism, paroxysmal atrial fibrillation, and vaginal prolapse following a prior hysterectomy presented to the emergency department with weakness, lightheadedness, and 1 day of intractable, frequent bowel movements. The patient reported severe fecal urgency, with small bowel movements occurring every 10 minutes. She denied a history of recent constipation, abdominal pain, hematochezia, fever, or melena. She noted changes in her bowel movements consisting of occasional episodes of mild diarrhea dating back 6 months but no prior episode as severe as this one. These episodes had been investigated on an outpatient basis, with prior stool studies negative for clostridium difficile toxin, and a colonoscopy, which revealed only mild left-sided diverticuli.

Upon admission, the patient was found to be in atrial fibrillation. Her serum electrolytes, thyroid tests, complete blood count, cardiac enzymes, and liver function tests were all normal. Her physical examination was unremarkable except for a hard extrinsically protruding object detected on digital rectal examination. This object turned out to be a vaginal pessary, placed approximately 8 months before for treatment of urinary incontinence. A radiograph of the patient's abdomen demonstrating the location of the device is shown in Figure 1.

Upon removal of the pessary, the patient's symptoms resolved.

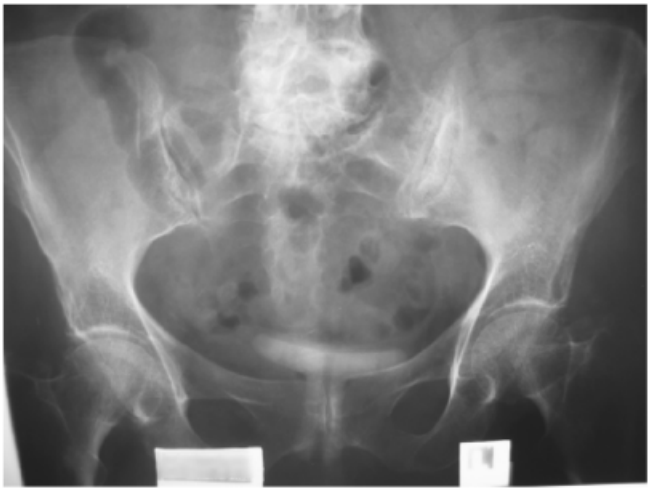

Figure 1. X-ray demonstrating the position of the vaginal pessary.

DISCUSSION

We have presented a case of fecal urgency, loose bowel movements, and incontinence caused by a vaginal pessary in an elderly woman. To our knowledge, there is only one other report in the literature of such an occurrence.[1]

There are several mechanisms by which this patient's symptoms may have been produced. First, the force of the pessary pressing on the rectal mucosa may have caused obstruction with paradoxical diarrhea, as occurs with fecal impaction. Secondly, when the pessary exerted pressure on normal anatomical features, such as the internal and external anal sphincter muscles, it might have stretched the anatomy and altered the normal mediators of fecal continence. Lastly, the presence of the pessary might have produced the sensation of full rectum, elucidating a defecation reflex.

The patient in this case had "pseudodiarrhea," which is defined as increased stool frequency (>3 daily) with a normal daily stool weight of less than 300 g. Conditions commonly associated with pseudodiarrhea include paradoxical diarrhea secondary to fecal impaction and irritable bowel syndrome.

Physicians should be aware that there are many different symptoms that patients term as "diarrhea," and these should be differentiated in the history taking. They include fecal incontinence, urgency, liquidity of the stool, frequency, and volume of stool. Patients are likely to define diarrhea as stool liquidity. The strict scientific definition of diarrhea is stool quantity greater than 300 g/d, although most clinicians generally also consider increased stool frequency (>3/d) as part of the definition.[2]

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ACUPUNCTURE FOR DYSPHAGIA IN POSTSTROKE PATIENTS: A VIDEOFLUOROSCOPIC STUDY

To the Editor: Severe dysphagia predisposes to medical complications such as aspiration pneumonia in poststroke patients.[1] Existing modalities for treating dysphagia are generally ineffective.[2] It was recently reported that acupuncture on two acupoints (Zusanli ST36 and Taixi K3) restored the swallowing reflex[3] and gait disorders[4] in poststroke patients. In the current study, a videofluoroscopic study (VFSS) was performed to determine whether acupuncture also improves dysphagia and aspiration. According to magnetic resonance imaging findings, 32 poststroke patients (mean age $\pm$ standard deviation 84 ± 9; 20 women, 12 men) with episodes of choking while eating or drinking were selected randomly at an elderly care facility and participated in this study under written informed consent. Participants were randomly assigned to two groups. Acupuncture was practiced on the intervention group (aged

77 ± 9; 10 women, 8 men) three times a week for 4 weeks with usual care. Four disposable stainless steel fine needles (0.16 mm diameter, 40 mm length; SEIRIN, Shizuoka, Japan) were inserted in two acupoints (ST36 and K3) bilaterally and kept at a 10 mm depth for 15 minutes without any extra electrical or manual stimulation. Fourteen other patients were assigned to the control group (aged 79 ± 5, 10 women, 4 men) and received usual care without acupuncture. VFSS was performed at baseline and 4 weeks later in both groups. The interval of VFSS was 5 minutes, with a random order of three different kinds of food. The patients were asked to swallow 5 mL of water, 5 mL of fluid food (liquefied food), and one piece of solid food (approximately 5 mL of a cookie). The water and food were blended with barium (Enemastar Enema Powder, FUSHIMI Pharmaceutical, Marugame, Japan). In each swallowing, VFSS was performed in a lateral projection with the patient seated using a fluoroscopy unit (Prestige, GE Medical Systems, Tokyo, Japan) connected to a digital video disk—hard disk drive recorder (RD-XS30, Toshiba, Tokyo, Japan). Images were obtained at 30 frames per second and reviewed frame by frame using image-processing software (Premier 6.0, Adobe Systems, Tokyo, Japan) by a radiologist who did not know whether the patient had been treated with acupuncture. Pharyngeal retention was defined as pharyngeal residue of material in the valleculae and in the piriform sinuses after swallowing. Tracheobronchial postdeglutitive aspiration was defined as penetration of material below the level of the vocal folds. VFSS frames from the instruction of swallowing to the time that the material passed the entrance of the esophagus were observed. Body temperature was measured at 2:00 p.m. every day. The total number of days of fever above 37.8°C was summed for 4 weeks. The mean swallowing time ± standard deviation at baseline from the instruction to swallow to the time the water, fluid food, and solid food passed the entrance of the esophagus was 1.7 ± 1.0, 8.7 ± 13.2, and 10.4 ± 7.0 seconds, respectively, in the intervention group and 1.9 ± 0.6, 4.5 ± 3.7, and 9.7 ± 7.6 seconds in the control group. After 4 weeks, the average time was 1.1 ± 0.3 ($P < .05$), 5.0 ± 4.8 ($P < .05$), and 11.8 ± 9.3 seconds, respectively, in the intervention group and 2.1 ± 0.9, 5.4 ± 5.4, and 10.1 ± 6.9 seconds in the control group. In the intervention group, the swallowing time of water and fluid food were shortened significantly after 4 weeks. Figure 1 shows the percentage of pharyngeal retention and aspiration in the two groups. In the intervention group, there were significant decreases in retention; in the control group there was no significant change. In the intervention group, aspiration at the baseline was observed in 40%, 8%, and 25% of the patients with water, liquid, and solid foods, respectively, but no aspiration was observed after 4 weeks. Aspiration did not change in the control group after 4 weeks. Fever greater than 37.8°C was observed on 28 of 394 days in the control group but only on 4 of 356 days of the intervention group. The intervention group had significantly fewer days with high fever than did the control group ($P < .01$). The combination of these acupoints, which are novel, safe, and easy to use, was selected according to the traditional theory of Chinese medicine. These data show the significant effect of the acupuncture treatment on pharyngeal retention and aspiration. The present study suggests that this acupuncture therapy is a new way to prevent aspiration and aspiration pneumonia in poststroke patients.

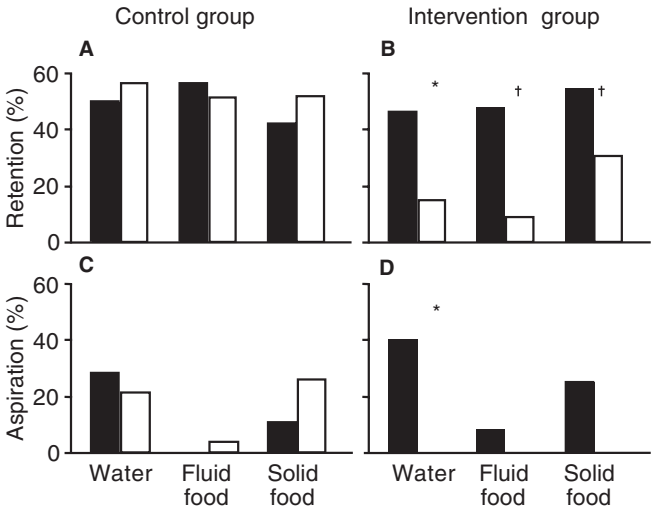

Figure 1. The rate of pharyngeal retention (A, B) and aspiration (C, D) in the control and intervention groups at baseline (closed column) and after 4 weeks (open column). Significant decreases after 4 weeks compared with baseline according to Wilcoxon signed rank test; $P < *.05$ and $^{\dagger}.01$.

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