A SUDDEN AND TEMPORARY EPISODE OF ALTERED MENTAL STATUS: A CASE REPORT

To the Editor: Altered mental status is a frequent cause of admission to the emergency department, and diagnosis is always a difficult task. In a recent retrospective review of the medical records of a university hospital,[1] the most common discharge diagnoses accounting for altered mental status were neurological (28%) and toxicological (21%), followed by trauma and psychiatric (14% each), infectious (12%), endocrine/metabolic (5%), and others (pulmonary, oncological, cardiovascular, gastrointestinal, and renal, all together accounting for 9%). This may also have implications for prognosis and survival. For example, nondetection of delirium in the emergency department has been shown to be associated with increased mortality.[2]

CASE REPORT

A 75-year-old man was admitted to the hospital for a short loss of consciousness followed by altered mental status. He was walking with his wife when he complained of an abrupt, transient loss of consciousness that lasted a few seconds. He first showed mental confusion and disorientation, then sudden irritability and verbal aggressivity.

His wife, frightened by the altered and threatening tone of voice, resembling Linda Blair in the movie *The Exorcist,* accurately reported the event. Duration was approximately 5 minutes, and the ambulance team described a normal mental status. No head trauma occurred. On hospital admission, the patient was in good health. Consciousness was clear, although there was complete amnesia of the event. Psychiatric assessment was normal.

Medical history included only mild hypertension, treated with the calcium channel blocker amlodipine, 10 mg/d. Blood pressure and heart rate were 140/90 mmHg, and 86 beats per minute, respectively. General appearance, neurological examination, and complete blood chemistry panel were normal. Computed tomography scan revealed a chronic subdural hematoma in the left frontal-parietal hemisphere (thickness: 1.5 cm, cranium-caudally spreading for 9 cm) (Figure 1). Neurosurgical operation was promptly and successfully performed, and the surgeon reported that the hematoma was not recent. Only a few days later, the patient, who had always denied any kind of trauma, remembered a minor head trauma that had occurred 5 months before at home.

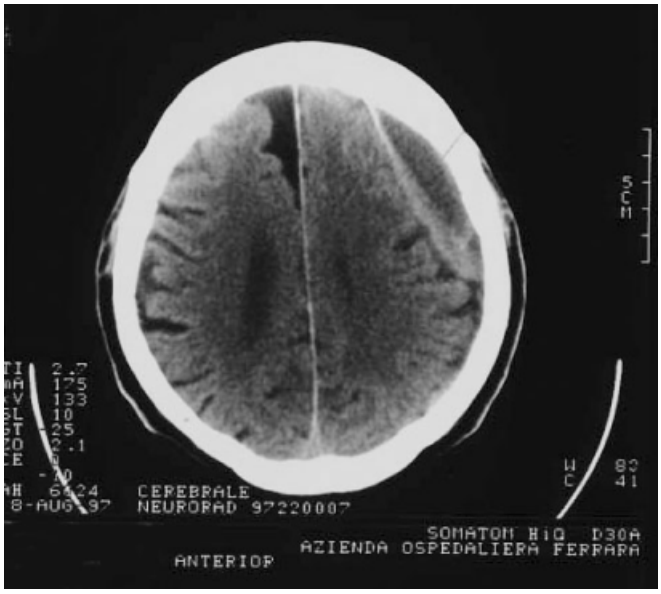

Figure 1. Computed tomography scan of the head showing a chronic subdural hematoma in the left frontal-parietal hemisphere.

DISCUSSION

In older patients, in the case of an acute change in mental status, the hypothesis of subdural hematoma must always be excluded, even if focal neurological findings are not present.[3] Chronic subdural hematoma is predominantly a disease of the elderly and usually follows a minor trauma, although a history of direct trauma to the head is absent in up to half the cases.[4] The causative injury may be trivial and is often forgotten because it was remote in time. A period of weeks, or even months, follows when headaches, slowed thinking, confusion, change in personality, seizures, or mild hemiparesis are the main findings.[5] The most common manifestations are altered mental status and focal neurological deficit, but a wide diversity of features is observed in adults, often simulating other neurological and psychiatric diseases. This is particularly problematic in the elderly, for whom more nonspecific clinical presentations are common,[6] and computed tomography remains the most useful tool.[7] Careful recognition of even poor and misleading clinical features, including transient changes in personality, is crucial. A prompt diagnosis allows for the prevention of delays that may lead to increased morbidity in these patients, for whom neurological state at time of diagnosis is the most important prognostic factor.[4]

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0002-8614/05/$15.00

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EXERCISE-RELATED SYNCOPE INDUCED BY VASODILATOR THERAPY IN AN ELDERLY HYPERTENSIVE PATIENT

To the Editor: Although vasodilators such as angiotensin I-converting enzyme inhibitors (ACEIs) and calcium channel blockers, singly or in combination, are widely used for the treatment of hypertension, they are known to impair hemodynamics and may lead to hypotension and cardiovascular events in elderly hypertensive patients with a small left ventricular cavity (SLVC) due to severe left ventricular hypertrophy.[1] Furthermore, chronic vasodilator therapy in elderly hypertensive patients could impair baroreflex compensatory mechanisms, which may become unable to restore a sufficient systemic and cerebral blood flow.[2]

CASE REPORT

A 72-year-old woman was admitted to our hospital because of syncope. She had been diagnosed with hypertension at the age of 60, which had been treated with a combination of temocapril hydrochloride (2 mg) and amlodipine besilate (5 mg) for the previous 3 years. Secondary hypertension was excluded by scrutiny. She had had presyncope several times on physical exertion over the previous 6 months and had had syncope while working at home on the morning of admission. On admission, her level of consciousness was

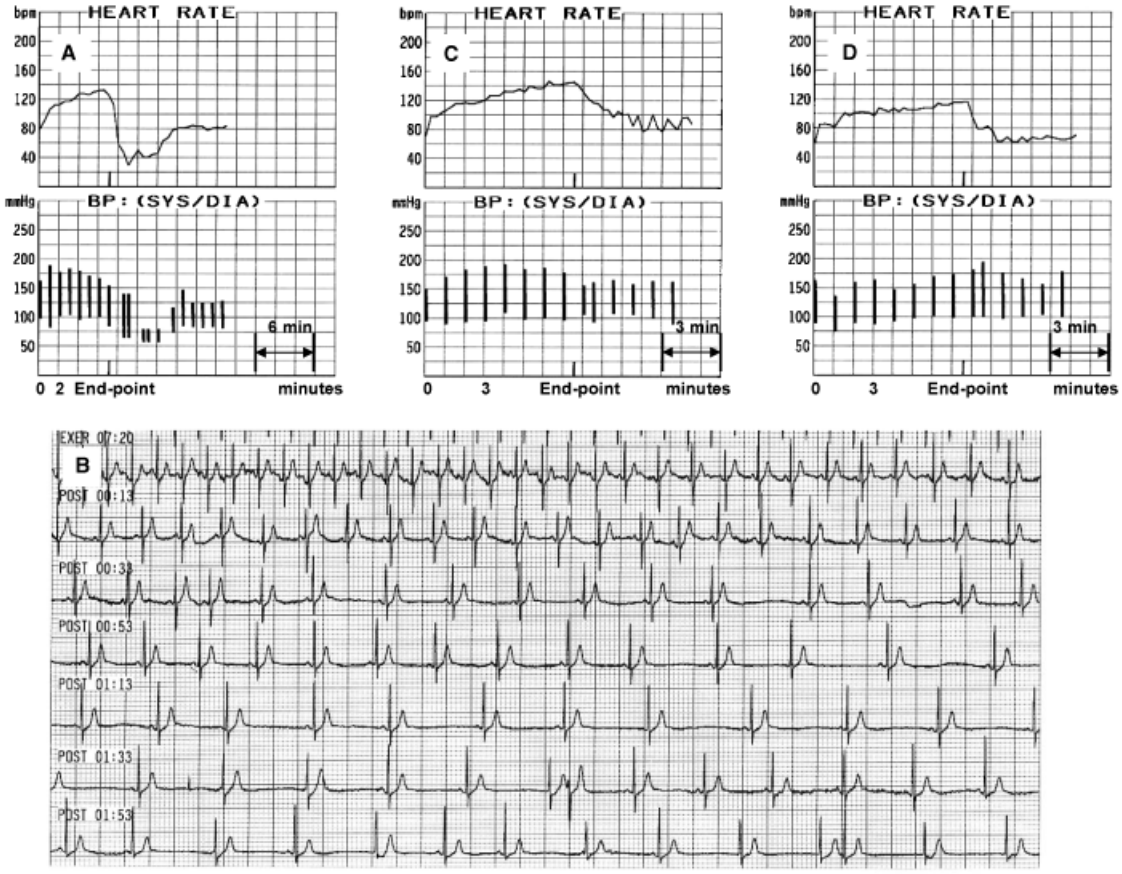

Figure 1. Treadmill test (Bruce protocol). (A) Treadmill test under administration of temocapril hydrochloride (2 mg/d) and amlodipine besilate (5 mg/d). Sudden hypotension and bradycardia occurred during the postexercise recovery period. The exercise time was 7 minutes, 30 seconds. The endpoint was leg fatigue.
(B) Rhythm strip between exercise at 7 minutes, 20 seconds and the postexercise recovery period at 2 minutes, 3 seconds. Bradycardia due to sinus arrest and a junctional escape rhythm appeared during recovery from exercise.
(C) Treadmill test without drugs. No abnormal findings were present. The exercise time was 7 minutes, 30 seconds. The endpoint was the target exercise time.
(D) Treadmill test after administration of metoprolol tartrate (40 mg/d). No abnormal findings were present. The exercise time was 7 minutes, 30 seconds. The endpoint was the target exercise time.

normal. Her blood pressure was 124/74 mmHg in a supine position. Physical examination revealed no abnormal findings except for a pulse rate of 40 beats per minute with irregularity. Laboratory levels were within normal limits. Electrocardiography showed bradycardia due to sinus arrest and a junctional escape rhythm without significant ischemic ST-T changes. Sinus rhythm was restored only with rest. Echocardiography showed an SLVC due to concentric left ventricular hypertrophy and an abnormal left ventricular relaxation pattern. Peak A-wave and peak E-wave velocities measured from transmitral pulsed-wave Doppler flow recordings were 0.93 m/s and 0.51 m/s, respectively, which suggested left ventricular diastolic dysfunction. Coronary angiography revealed no organic stenosis. Left ventriculography demonstrated an SLVC and no wall motion asynergy. The calculated end-diastolic volume, end-systolic volume, and ejection fraction were 60 mL, 19 mL, and 69%, respectively. Overdrive suppression of the sinus node with intracardiac pacing showed a normal sinus node recovery time, excluding the possibility of sick sinus syndrome. Passive head-up tilt test revealed no abnormal findings. A treadmill test after administration of temocapril hydrochloride (2 mg) and amlodipine besilate (5 mg) disclosed sudden hypotension and bradycardia due to sinus arrest and a junctional escape rhythm during the postexercise recovery period (Figure 1A, B) that led to presyncope. She made a slow recovery after returning to the supine position. Administration of these drugs was stopped because it was thought that vasodilators might trigger presyncope. In the absence of these medications, treadmill test did not provoke presyncope (Figure 1C), but 24-hour ambulatory blood pressure monitoring showed poorly controlled hypertension without antihypertensive agents. Metoprolol tartrate (40 mg/d) was administered, and treadmill test did not provoke presyncope (Figure 1D). Subsequently, she has remained free of recurrent syncope after 9 months of follow-up.

DISCUSSION

Whether vasodilators induce exercise-related syncope remains unclear. Her usual symptoms could be replicated by treadmill test. Cessation of vasodilators and the initiation of a beta-blocker relieved her symptoms. Venous pooling after exercise was reported to be one of the mechanisms triggering sinus arrest.[3] A decrease in venous return after exercise along with elevated sympathetic tone and increased levels of circulating catecholamines may result in extremely vigorous ventricular contraction. This action activates a number of afferent mechanoreceptor (C-fibers) in the base of the ventricles.[4] This increase in afferent neural activity with subsequent baroreceptor unloading can produce baroreceptor-mediated vasodilation and further hypotension.[5] Vasodilators may lower the threshold to trigger an abnormal vagal afferent response to decreased venous return, especially in elderly hypertensive patients with an SLVC. In fact, vasodilators were shown not to be helpful and were even dangerous in elderly hypertensive patients with an SLVC.[1] In addition, impaired baroreflex compensatory mechanisms due to chronic vasodilator therapy[2] may trigger syncope. Although ACEIs were reported to prevent neurally mediated syncope in a small population (mean age 37.6),[6] careful attention must be paid to their use in elderly hypertensive patients with an SLVC. The left ventricular diastolic dysfunction in this patient was compatible with hypertensive heart disease and aging. This diastolic dysfunction might not affect her symptoms directly because the transmitral Doppler flow pattern did not improve by changing drugs.

We report a case of a 72-year-old hypertensive woman with exercise-related syncope induced by vasodilators. This syncope was treated with the cessation of vasodilators and the initiation of a beta-blocker. We must be cautious about vasodilator therapy for treatment of hypertension in elderly hypertensive patients with an SLVC.

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DISTRIBUTION OF GYNECOPATHOLOGICAL FINDINGS IN GERIATRIC WOMEN

To the Editor: On the basis of epidemiological data, geriatric women have a high chance of harboring genital malignancy as well as other organ malignancies.[1–3] Clinicians treating women should have knowledge of the fact that genital malignancies have to be properly screened, enabling an early diagnosis and treatment. This retrospective study was planned to document 218 histopathological diagnoses of tissue specimens obtained from geriatric women after gynecological surgery between 1999 and 2003. Histopathological results were then grouped, based on tissue origin, as nonneoplastic, neoplastic, and other pathologies such as borderline ovarian tumor, intraepithelial cervical or vulvar/vaginal lesions, and endometrial hyperplasia. The surgical stages of all genital malignancies were not specified; the aim was to demonstrate only the distribution of all genital pathologies.

Of 218 histopathologic results, the majority of pathologies originated from the endometrium (n = 120, 55%) and the ovary (n = 35, 16%). Gynecological malignancy was

Table 1. Distribution of Final Gynecopathological Diagnosis in Geriatric Women After Surgery

Organ	Nonneoplastic	Benign Neoplastic	Intraepithelial Lesion	Borderline	Malignant	n
	n (%)					
Endometrium	14 (15)	34 (36)	—	—	46 (49)	94 (100)
Myometrium	5 (19)	12 (46)	—	—	9 (35)	26 (100)
Ovary	9 (26)	6 (17)		1 (3)	10 (28)	35 (100)
Cervix	16 (46)	8 (23)	—	—	10 (28)	35 (100)
Vulva	7 (30)	8 (35)	2 (9)	—	6 (26)	23 (100)
Vagina	1 (20)	3 (60)	—	—	1 (20)	5 (100)
Total	52 (23.9)	71 (32.6)	3 (1.3)	1 (0.5)	91 (41.7)	218 (100)

encountered in 91 (41.7%) of all documented histopathological results. Distribution of all genital malignancies and their percentages are summarized in Table 1. Detailed documentation of 120 uterine pathologies (94 endometrium and 46 myometrium) were as follows.

In terms of ovarian pathologies, nine (26%) nonneoplastic (two tuberculosis, one simple cyst, one epithelial inclusion cyst, five serous cysts), six (17%) benign neoplastic (three fibroma, one mucinous cystadenoma, one serous cystadenoma, one benign cystic teratoma), one (3%) mucinous borderline tumor, and 19 (54%) malignant neoplastic (12 serous carcinoma, one mucinous carcinoma, two endometrioid carcinoma, two clear cell carcinoma, one undifferentiated carcinoma) lesions were observed.

Of 35 cervical pathologies, 16 (46%) cases revealed nonneoplastic lesions (three unspecified histopathologic changes, 13 chronic cervicitis) and eight (23%) cases harbored benign neoplastic lesions (eight cervical polyp). Cervical intraepithelial lesion was observed in one case (3%), whereas invasive cervical cancer (seven squamous cell carcinoma, two adenocarcinoma, one adenosquamous carcinoma) changes were relevant in 10 (28%) cases.

In this study, approximately 1.3% (28/281) of cases had vulvar (n = 23) and vaginal (n = 5) malignancies. Vulvar pathologies showed seven (30%) nonneoplastic lesions (four lichen sclerosis, one seborrheic dermatosis, one epidermal inclusion cyst, and one chronic inflammatory process), eight (35%) benign neoplastic lesions (six squamous cell hyperplasia, two intradermal nevus), two (9%) vulvar intraepithelial lesions (one vulvar intraepithelial neoplasia (VIN)-III and 1 VIN-II), and six (26%) malignant neoplastic lesions (five squamous cell carcinoma, one verrucous carcinoma). Of vaginal pathologies, one (20%) had nonneoplastic lesions (simple cyst). In addition, three (60%) cases had benign neoplastic changes (two polyp, one basal cell hyperplasia) and one (20%) case revealed malignant neoplastic changes (malignant mesodermal tumor).

When an older woman develops one of these malignancies, she is more likely to die from malignancies than a younger woman.[2] The majority of elderly women do not have regular gynecological follow-ups, leading to a subsequent increase in the number of malignant diseases diagnosed at advanced clinical stages.[4] Furthermore, associated medical problems limit the possibility of operative treatment. Because elderly women tolerate most surgical approaches, chemotherapy, and radiotherapy well, studies should be directed toward improving screening, care, and treatment of the elderly population, which will decrease the significant morbidity and mortality associated with genital malignancies.[2,5] It has been pointed out that the most-often-diagnosed malignant neoplasm in women aged 70 and older was endometrial cancer.[6] In our study, mean ages ± standard deviation of cases with endometrial and ovarian cancer cases were 68.4 ± 2.2 and 70.1 ± 1.8, respectively.

According to our study, 35 of 91 (11%) cases with genital malignancy had invasive cervical cancer. In this regard, periodic cervical screening via cytology is essential for early diagnosis and treatment of cervical cancer. It has been observed that older women were less likely than younger women to have been screened within 3 years before cancer diagnosis.[7] Several studies have addressed this issue, indicating that cervical cancer screening efficacy declines with older age.[8,9] Another challenge is that, in addition to a decline in the periodic admission rates of elderly women to gynecology clinics, lack of healthcare-provider recommendation constitutes one of the major predictor of underutilization of cervical cancer screening.[10]

This study has demonstrated that the majority of genital pathologies were malignant and endometrial and ovarian in origin. Hence, public health policies and care providers should collaborate in developing national strategies and guidelines to facilitate genital cancer screening and to increase the admission rates to gynecology clinics for a satisfactory disease-free life expectancy and a better quality of life.

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ANOREXIA AS AN INDEPENDENT PREDICTOR OF MORTALITY

To the Editor: In the elderly, anorexia could be a direct consequence of many chronic diseases, but it was not until 1988 that Morley and Silver defined the syndrome "anorexia of aging" as a physiopathological decline in food intake with aging that predisposes older persons to develop protein-energy malnutrition when certain psychosocial factors and diseases are concomitant.[1] This decline has also been seen in disease-free ambulant older persons.[2] The relationship between anorexia of aging and malnutrition has been largely reviewed,[1,3,4] but the prognostic relevance of this symptom on mortality independent from biochemical indices of nutrition has never been studied.

This preliminary study analyzes whether anorexia of aging could be a predictor of mortality, independent of indices of malnutrition, illness severity, comorbidity, and cognitive and functional status.

All consecutive patients discharged from a Geriatric Evaluation and Rehabilitation Unit (Richiedei Medical Center, Palazzolo s/O—Brescia, Italy) were considered. Patients underwent a multidimensional assessment to evaluate cognitive, mood, functional, nutritional, and somatic health status. Particular attention was paid to anorexia, which was detected by asking relatives upon admission, "During the last three months, was food intake decreased for whatever the cause?" from the Mini Nutritional Assessment (MNA).[5] This sample question was submitted separately to 20 pairs of caregivers to evaluate its validity. The first caregiver's answer was compared with that of the second one, and interrater reliability was analyzed using the Spearman correlation coefficient (rho = 0.79, $P < .001$). Moreover, a week after the admission, the first relative was asked again, and the answer was compared with the previous one (test-retest) (rho = 0.91, $P < .001$).

Because current criteria for diagnosis of anorexia of aging do not exist, to study anorexia of aging (not related to disease), patients with the highest severity of all diseases (Individual Disease Severity Index[6] (IDS IV)) or with moderate severity (IDS III) of conditions directly or indirectly associated with dyspepsia or poor food intake (cancer, cardiopulmonary, gastrointestinal, hepatobiliary, and renal diseases) were excluded.

After discharge, data on mortality were collected by telephoning the family or the Mortality Register. Patients were observed for a median of 10.5 months (25th–75th percentiles = 6.0–15.5 months). The final sample consisted of 316 patients; 50 (15.8%) were affected by anorexia.

In Table 1, the characteristics of the selected population are shown; patients with anorexia of aging are older and have a greater risk of malnutrition (MNA), and the percentage of subjects with weight loss is higher. According to cognitive and functional status, the two groups were not different. Taking into account some biochemical indices, anorectic patients had a lower level of serum albumin and transferrin, but total cholesterol and ferritin were similar. The prevalence of somatic chronic diseases was analogous in the groups. Mortality of patients with anorexia was

Table 1. Characteristics of 316 Selected Patients Discharged from the Richiedei Geriatric Evaluation and Rehabilitation Unit and Divided According to the Presence of Anorexia

Characteristic	No Anorexia (n = 266)	Anorexia (n = 50)	*P*-value*
Age, mean ± SD, years	76.5 ± 6.8	81.0 ± 7.2	.000
Male, n (%)	59 (22.2)	9 (18.0)	.326
Mini-Mental State Examination score mean ± SD (range 0–30)	22.7 ± 5.6	21.7 ± 5.9	.249
GDS score, mean ± SD (range 0–15)†	6.2 ± 3.4	6.4 ± 3.5	.711
Depression, n (%)	64 (24.1)	18 (36.0)	.058
Barthel Index, mean ± SD (range 0–100)	67.9 ± 23.6	60.0 ± 29.2	.073
Tinetti Scale, mean ± SD (range 0–28)	15.7 ± 8.6	14.3 ± 9.4	.289
Burden of Disease score, mean ± SD (range 0–64)	9.1 ± 3.5	9.9 ± 4.3	.125
Number drugs on discharge, mean ± SD	5.5 ± 2.2	5.4 ± 1.9	.834
Mini-Nutritional Assessment score (screening), mean ± SD	11.1 ± 2.3	8.6 ± 2.9	.000
Weight loss of ≥3 kg/3 months, n (%)	41 (15.6)	15 (30.0)	.016
Serum albumin, mean ± SD, g/dL	3.6 ± 0.4	3.5 ± 0.4	.011
Transferrin, mean ± SD, mg/dL	221.7 ± 43.3	200.2 ± 46.7	.002
Ferritin, mean ± SD, ng/mL	172.5 ± 195	174.1 ± 139.7	.957
Total cholesterol, mean ± SD, mg/dL	188.1 ± 36.8	187.4 ± 43.6	.912

*Significance on *t* test or chi-square test between no-anorexia and anorexia groups.
†Depression was considered clinically present if Geriatric Depression Scale (GDS) score >9/15.
SD = standard deviation.

higher than patients without this symptom (16.0% vs 6.4%, $P<.05$). The relationship between anorexia and mortality was analyzed using the model of Cox regression analysis, including age, Mini-Mental State Examination, depression (Geriatric Depression Scale score $\geq$9/15), Barthel index, gastrointestinal and hepatobiliary diseases, Burden of Disease[7] (sum of IDS score of 16 chronic diseases), MNA, weight loss ($\geq$3 kg/3 months), serum albumin, and transferrin, which are possible mediators of the link between poor food intake and survival. Anorexia (hazard ratio (HR) = 2.9 95% confidence interval (CI) = 1.1–7.4) and Barthel index (HR = 1.1 95% CI = 1.0–1.2) were found to be independent predictors of mortality. The risk of mortality was three times higher in the anorectic subjects, after adjusting for possible causes or the direct consequence of poor food intake.

The advantage of investigating food intake reduction is supported by the fact that it is a simple self-reported or caregiver-reported symptom. Recently, clinicians have been urged to regularly evaluate nutritional risks using questionnaire such as the MNA,[1] and the need for simple, reliable, and valid tools, based on self-report and applicable in a variety of settings has been underlined.[8] A clinical evaluation of nutritional risk in the multidimensional assessment may promote therapeutic interventions by identifying and treating underlying diseases, increasing the quality of nursing feeding assistance, and planning early nutrition rehabilitation and education programs for caregivers,[3,9,10] although the efficacy of these interventions is controversial. Perhaps the detection of early risk factors of malnutrition, such as anorexia, could increase the probability of success of nutritional interventions in target elderly subjects.

In conclusion, we found that anorexia (not directly associated with chronic diseases) is an easy way to identify subjects particularly likely to have higher mortality independent of malnutrition.

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POLYMYALGIA RHEUMATICA AND MALIGNANCY: THE QUESTION REMAINS OPEN

To the Editor: Recently Martin et al. reported the case of an elderly woman with hematological malignancy associated with polymyalgia rheumatica (PMR).[1] They concluded by questioning a true paraneoplastic relationship between both diseases and postulated a chance association. An elderly man who presented with PMR several months before diagnosis of colon carcinoma is described. The PMR symptoms were resolved after colectomy.

A 69-year-old man presented with a 5-week history of pain and moderate stiffness in his shoulder and hip girdles, limitation of mobility, and fever. There was no history of headache, visual changes, jaw claudication, anorexia, or weight loss. Medical history was unremarkable. Physical examination revealed a temperature of 37.9°C but no signs of temporal arteritis, synovitis, muscle weakness, or atrophy. Laboratory data showed erythrocyte sedimentation rate (ESR) of 92 mm/h, C-reactive protein of 14 mg/dL, and hemoglobin of 11.9 g/dL. A temporal artery biopsy was negative. The patient, who was diagnosed with PMR, was prescribed 25 mg of prednisone daily. One week later, he became afebrile, and pain and stiffness had significantly decreased, but ESR remained persistently raised and PMR kept recurring with dose reduction. Ten months after discharge, the patient presented with sanguinolent diarrhea. Examination showed moderate pain to pressure on lower left quadrant. Laboratory data showed hemoglobin level of 6.8 g/dL and ESR of 60 mm/h. A colonoscopy and barium enema revealed a neoplastic lesion in the cecum with histological study corresponding to adenocarcinoma. There were no metastases. A colectomy with radiotherapy was performed. Corticosteroid therapy was stopped, and disease remission was achieved. Four years later, he is doing well.

Classical PMR is an idiopathic disorder affecting mostly elderly people. Occasionally the diagnosis may be a challenge because PMR appears associated with malignancy.[2,3] This association is known as paraneoplastic PMR, and its reported prevalence is low.[4] Some problems may be found in diagnosis of PMR, mainly nonspecific presentation and lack of definitive diagnostic criteria.[5] Also, a large variety of tumors could appear as paraneoplastic rheumatic

syndromes. Paraneoplastic PMR has to be differentiated from atypical PMR, which complicates metastatic cancer.[6] Whether both diseases occur by chance or have a cause-effect relationship has long been a subject of discussion. Some authors postulate that a chance occurrence based on these disorders appears mainly in elderly patients and that no increased risk of malignancy has been found in prospective and retrospective studies,[2,4,7,8] but a possible bias of prior selection due to exclusion of disorders presenting with PMR-like symptoms such as malignant neoplasm has to be taken in account.[9] This may explain the low prevalence of association. To overcome this problem, a prospective study with no patient selection was begun.[9] A highly significant difference between the observed incidence of cancer in the PMR group and the age- and sex-adjusted prevalence of malignancy in the population was seen. In addition, a hazard rate for developing malignancy in patients with positive biopsy temporal arteritis, a disorder commonly related to PMR, was 2.35 times higher than in the controls.[7] Strong evidence of a true causal relationship has been suggested in some cases in which PMR resolution was achieved after treatment of neoplasia.[3,10] Thus, it may be hypothesized that, in this reported patient, PMR was a paraneoplastic manifestation of his underlying carcinoma, and it is possible that both diseases were pathogenetically related. Because the long discussion about "chance or causality" appears far from finished, to opt for one of the two hypotheses was unremarkable. What is important is the development of an appropriate index of suspicion in the presence of an incomplete response to treatment, and further evaluation for paraneoplastic PMR should be considered. Although Martin et al. believe that an answer has been found,[1] the question is open.

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TENNIS LEG: A LOOK FROM THE GERIATRIC SIDE

To the Editor: A 60-year-old man (a taxi driver) was seen for complaints of acute swelling and severe pain in his left calf. He declared that the complaints ensued while he was lifting a 20 kg to 30 kg weight. His medical history was unremarkable for any systemic disorders or medications. Physical examination revealed a swollen, tender, ecchymotic medial compartment of the left leg. The knee and the ankle joint motions were painful, especially during passive ankle dorsiflexion. An immediate ultrasonography depicted hemorrhage in the gastrocnemius muscle. Magnetic resonance imaging confirmed (Figure 1). He was diagnosed with a rupture in the medial head of the gastrocnemius muscle and was treated conservatively with rest, intermittent cold application, and a nonsteroidal antiinflammatory drug. Later, exercises were introduced gradually, starting with passive stretching and moving to exercises for antagonist, agonist, and quadriceps strengthening.

Rupture of the gastrocnemius muscle is usually seen in athletes, especially those involved with side-to-side sports, and thus is referred to as "tennis leg."[1] It is an uncommon type of injury in otherwise healthy individuals.[2] The differential diagnosis can sometimes be challenging[3–5] and necessitate further imaging.[6,7] The treatment is mainly conservative; its prevention and rehabilitation entail stretching and strengthening exercises. In this report, we had an older man who had suffered tennis leg during strenuous weight lifting in daily life. We underscore the fact that the injury might become more likely in the elderly because the degenerative changes at the myotendinous junctions decrease the

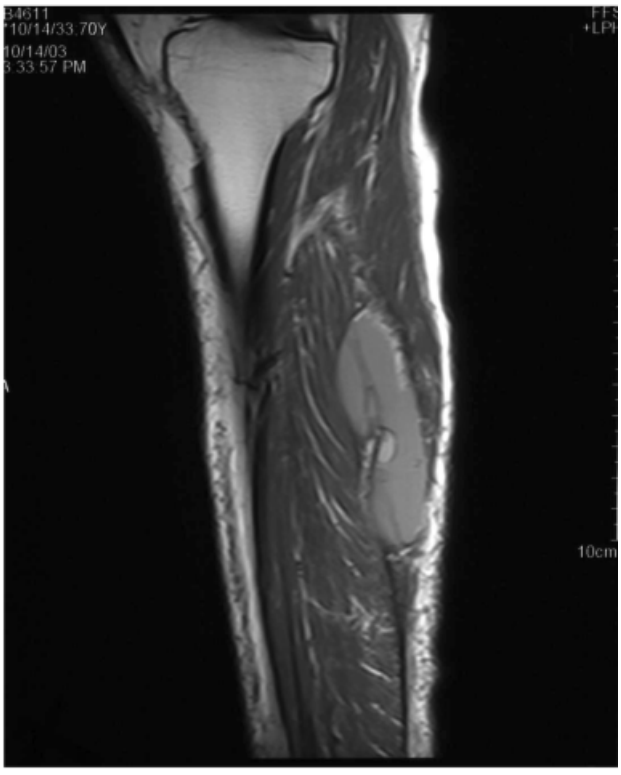

Figure 1. Magnetic resonance imaging (sagittal view) of the calf depicting the rupture and the hematoma in the gastrocnemius muscle.

muscle strength and predispose to rupture during activity.[8] Consequently, we recommend stretching and strengthening exercises for the calf muscles, which are subject to forces in daily life, in addition to the quadriceps strengthening exercises usually prescribed in the elderly for osteoarthritis.

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FAMILIAL LONGEVITY: THE OLDER YOU ARE, THE OLDER YOUR FATHER MAY HAVE BEEN

To the Editor: Lifespan in higher species reflects numerous specific genetic effects (e.g., "killer genes," lengths of telomeres, and mediation by genetic influences on life-shortening diseases and conditions). The heritability of longevity is complex, and biologists, population geneticists, evolutionists, and demographers have repeatedly examined the familial component of age at death in humans over the last century. In a classic study by Pearl, published in 1931, small but significant parent-offspring correlation in longevity was recorded in five large New England families.[1] A number of population-based and twin studies have also established a significant but modest familial component of human longevity; heritability estimates of age at death are reported to vary greatly ($<1\% - 35\%$).[2] These variations are the result of numerous interacting factors (e.g., genetic, environmental, and behavioral components) that are associated with the observed individual lifespan irrespective of their relationship to genetic predisposition to longevity. Moreover, differences in the types of paired relationships elucidated and the time periods and number of generations considered have affected the variation in heritability estimates in previous studies. According to the literature, sibling-sibling and parent-offspring paired relationships have the strongest association with reference to familial longevity.[3] Furthermore, in certain disorders, an association between familial longevity and prognosis has been recorded, although not consistently.[4,5] The present study was performed to assess the effect of maternal versus paternal longevity with regard to the cases' lifespan. To minimize potential influence from varying intraindividual environmental and behavioral components, a homogenous birth cohort (born in 1887) including 193 individuals randomly selected from two small farming villages (Pitea landskommun and Normaling) in northern Sweden was identified. The index cases and their parents were judged to have lived their lives in neighborhoods similar with respect to living and working conditions and with limited influence of urban lifestyle. Inclusion criteria were defined during the planning stage of the study, and cases were included accordingly: Cases had to be dead at younger than 75 (n = 93) or 90 and older (n = 100). Individuals who died before the age of 60 were not included in the present study because we were interested in reducing the effect on the analyses of familial aggregation of mortality that resulted from predisposition to particular diseases, such as heart disease, cancer, and diabetes mellitus. Data regarding date of birth and death for cases and their parents (n = 383, 99%) was retrieved from parish offices. Analysis of variance (*t* test) was applied to determine whether age at death was statistically different in parents of cases dying at a young age and parents of cases dying at an old age. *P*-values less than .05 were considered statistically significant. The

Table 1. Average Parental Age at Death According to Case's Age (Years) at Death

Case's Age at Death	N*	Parents' Age at Death		
		Father	Mother	Combined
		Mean ± Standard Deviation		
60–75	93	68.9 ± 13.8	70.4 ± 14.9	69.6 ± 11.4
≥91	100	71.3 ± 13.9	70.9 ± 15.6	71.4 ± 10.5
60–64	11	64.4 ± 17.0	66.3 ± 12.5	65.3 ± 8.0
65–75	82	69.5 ± 13.3	71.0 ± 15.2	70.2 ± 11.6
91–95	75	70.2 ± 14.6	70.3 ± 16.4	70.5 ± 10.6
≥96	25	74.5 ± 10.9	72.7 ± 13.3	74.0 ± 9.6

*Father unknown for one subject in the young group and two subjects in the old group.

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 ≥ 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 (≥ 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.

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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).[1] Sympathoadrenal activation, which is believed to act as a self-protective mechanism against an abrupt fall in plasma glucose,[2] 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 μU/mL to a peak level of 317 mg/dL and 215 μU/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[3] (Figure 1). In contrast, thallium-201 SPECT distribution was normal.

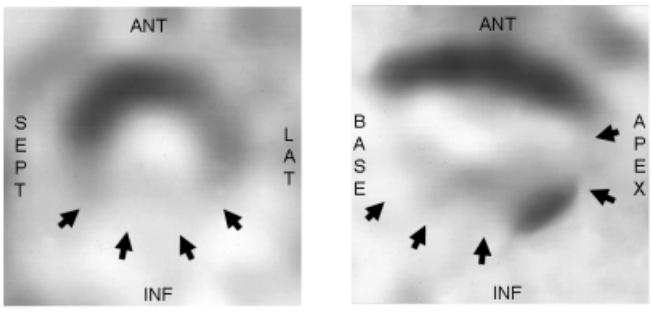

Figure 1. Clear defects of diffuse myocardial meta-iodobenzylguanidine (MIBG) uptake on iodide-123-MIBG single photon emission computed tomography (SPECT) imaging were observed (arrows). The left panel shows an axial view; the right panel shows an apical view of the left ventricle. ANT = anterior; LAT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

A diagnosis of late dumping syndrome with idiopathic autonomic failure was made,[4] and the patient was referred for acarbose treatment.[5] 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.[6] A previous report showed that acarbose attenuates postprandial reactive hypoglycemia and improves symptoms in patients with dumping syndrome.[5] 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.

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OPTIMIZING ANTILIBIDINAL TREATMENT WITH MEDROXYPROGESTERONE ACETATE

To the Editor: Sexual disinhibition in demented patients is not a common problem[1–3] 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.[3,4] 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.[2] Although there is some contrary evidence,[5] 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[3] used a fixed dose of 300 mg weekly, and Weiner et al.[4] 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[5] 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[6] reported testosterone levels reduced "nearly to female values" (25ng/dL–90 ng/dL,[7]) 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.

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DRUG-INDUCED LITHIUM INTOXICATION: A CASE REPORT

To the Editor: In their recent observation study, Juurlink et al. reported that the risk of lithium toxicity dramatically increased within a month of initiating treatment with a loop diuretic or an angiotensin-converting enzyme (ACE) inhibitor.[1] Besides pharmacokinetic drug interactions, interactions with psychotropic medications have been attributed to pharmacodynamic mechanisms.[2] We report a case of hospital admission for lithium toxicity secondary to drug interactions.

CASE REPORT

A 74-year-old woman was referred to us for a 3-week history of functional decline, lethargy, confusion, diarrhea, tremor, and dysarthria. Medical history included bipolar disorder, type II diabetes mellitus, hypertension, and ischemic heart disease. Medications on admission were lithium (250 mg three times daily), escitalopram (10 mg daily), levomepromazine (6.25 mg daily), lormetazepam (2 mg daily), metformin (850 mg three times a day), repaglinide (1 mg twice daily), lisinopril (30 mg daily), irbesartan (300 mg daily), furosemide (30 mg daily), and spironolactone (50 mg daily).

On admission, the patient was drowsy and confused. Glasgow Coma Scale was 12 of 15. Neurological examination showed dysarthria but no focal neurological deficits. Lithemia was 2.3 mEq/L (therapeutic range 0.6–1.2 mEq/L). Other investigations, including laboratory tests, computed tomography scan, and electroencephalogram, were not contributive. Serum creatinine was 161 μmol/L with an estimated clearance of 34 mL/min, secondary to dehydration.

Three months before admission, lisinopril dosage had been increased from 20 mg to 30 mg daily and irbesartan added for hypertension. Seven weeks before admission, spironolactone had been added. In addition, dexetimide 0.50 mg (a centrally acting anticholinergic drug licensed for the treatment of neuroleptic-induced extrapyramidal symptoms) had been recently added for worsening tremor, but no improvement was observed. Confusion had increased, and the drug was discontinued.

On admission, lithium was withdrawn, as were diuretics, levomepromazine, and escitalopram. Risperidone (0.25 mg twice daily) was added, but neurological status deteriorated with increased agitation, although the lithium level had fallen to 1.2 mEq/L on the fourth day after admission. Upon consultation, the clinical pharmacist proposed stopping potentially interacting drugs (lisinopril, irbesartan, risperidone) to accelerate lithium excretion and to eliminate neurotoxic symptoms. The patient was simultaneously transferred to the intensive care unit because of apathy and oliguria. Rehydration and withdrawal of interacting drugs led to substantial neurological improvement. The patient was discharged 2 weeks later on carbamazepine for maintenance treatment of bipolar syndrome. Two months later, the patient remains stable.

DISCUSSION

Risk factors for lithium toxicity include age-related altered pharmacokinetics, polypharmacy, and renal impairment. This case highlights the importance of stopping the causal drug but also drugs that may delay lithium elimination or worsen neurotoxic effects. Several drugs may have played a role in lithium intoxication. ACE inhibitors enhance the tubular reabsorption of lithium, and diuretics promote renal sodium wasting. They increase the risk of hospital admission for lithium toxicity.[1] The outcome of concurrent use of lithium and spironolactone remains unclear.[2,3] The addition of an angiotensin-II receptor antagonist (irbesartan) several weeks before admission may have contributed to lithium intoxication. The three case reports with candesartan, losartan, and valsartan that have been published indicate that intoxication can take several weeks to develop fully.[3] The mechanism of interaction is probably at least partially similar to that with ACE inhibitors. Finally, escitalopram and levomepromazine used with lithium may have increased the tremor associated with these drugs used alone.[4] It is also possible that a neurotoxic reaction occurred after the addition of risperidone. A similar observation has previously been reported.[3]

The equilibration of lithium between plasma and brain is extremely slow. Understanding this delay better enables the clinician to care for patients with lithium toxicity. Because clearance from the plasma is much faster than from the brain, it is not uncommon for patients who have presented with chronic lithium toxicity to still have signs of neurological toxicity when lithium concentrations have fallen into or below the therapeutic range.[5] This was the case here.

Inadequate monitoring of drug therapy can lead to a phenomenon called the "prescribing cascade."[6] The "prescribing cascade" begins when an adverse drug reaction is misinterpreted as a new medical condition. Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects. Dexetimide was added for worsening tremor probably secondary to lithium overdosage unrecognized at that time. This led to worsening neurological status. Geriatricians should be aware that a delay of several weeks between the addition of a new drug and lithium intoxication is possible.[2] Lithemia and clinical signs of overdosage should be monitored accordingly.

This case also illustrates that the contribution of clinical pharmacists is valuable in reducing drug-related morbidity and optimizing drug therapy.[7]

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CARDIAC DYSFUNCTION WITH SEVERE ANEMIA IN AN AGED CASE

To the Editor: On April 16, 2002, an 88-year-old woman was admitted to our hospital with complaints of easy fatigability and exertional dyspnea. Anemic conjunctiva palpebrae and pretibial edema were noticed on admission. Laboratory findings on admission showed white blood cell count 4,880/μL, red blood cells 131×10^4/μL, hemoglobin (Hb) 4.4 g/dL, hematocrit 12.9%, platelets 25.7×10^4/μL, reticulocytes 0.1%, serum creatinine 0.9 mg/dL, and serum iron 171 microgram/dL. Erythropoietin was highly elevated (2,860 mU/mL). Bone marrow examination showed severe hypoplasia specific for erythroid line (erythroid 0%), suggesting a diagnosis of pure red cell aplasia. Chest roentgenogram showed an enlarged heart with a cardiothoracic ratio of 60% and presence of pleural effusion, suggesting impaired cardiac function by severe anemia. Electrocardiogram (ECG) showed no abnormality except low amplitude of T-waves. Ultrasonocardiogram revealed reduced left ventricular ejection fraction and left ventricular dilatation at diastolic phase. Chest computerized tomography revealed relatively enlarged thymic mass (3 × 3 cm) for her age. As blood transfusion was performed to raise Hb level to 7 g/dL, pleural effusion and exertional dyspnea disappeared. Thymectomy was performed for treatment of pure red cell aplasia. After the thymectomy, cyclosporine A was administered. Hb gradually rose and reached 8.5 g/dL to 9.5 g/dL, accompanying normalization of erythropoietin (EPO) level (~20 IU/L). Cardiac function was promptly recovered, as shown by chest roentgenogram, ECG, and ultrasonocardiogram (Figure 1). Pretibial edema decreased gradually but did not completely disappear at 10 g/dL of Hb. EPO injection of 6,000 IU per week was started. About a month later, Hb level reached 14.0 g/dL, at which point she revealed no edema at all. During the additive EPO treatment, Hb level was within a range of 11 g/dL to 14 g/dL, and the improved cardiac function was maintained.

Although anemia is prevalent in old age, the minimum physiologically required value of Hb is potentially modifiable. Anemia is defined according to World Health Organization (WHO) criteria as a concentration below 12 g/dL in women and below 13 g/dL in men. Some studies report a particularly notable increase in prevalence of anemia in the oldest subjects ($\geq$85).[1–7] Even though normal Hb level can be deduced from mean value of Hb level of a healthy aged population, it is still unclear whether the mean value reflects a physiologically sufficient Hb level for aged organs. The present case showed that cardiac function was mostly normalized at 8.5 g/dL of Hb but sufficiently recovered and maintained in a range from 11 g/dL to 14 g/dL. Eleven g/dL of Hb seemed to be the minimum required Hb level for maintenance of normal cardiac function in this patient. In the present case, cardiac malfunction under severe anemic condition was evidenced clearly using ultrasonocardiogram. Anemia is a known risk factor for ischemic heart disease. The reduction in oxygen delivery by erythrocytes with anemia may be a cause of more severe cardiovascular diseases.[7,8] Nevertheless, in this case with severe anemia, ECG did not seem to reveal characteristic changes for presumptive tissue hypoxia such as ST depression or inverted T-wave. It has been reported that anemic condition accompanies ST-T depression or inverted T-wave,[9] but correlation between T-amplitude and Hb has not been reported. In the present case, the ratio of amplitude of T/QRS complex (T/QRS ratio) increased as Hb level increased. Although the other ECG parameters, including heart rate, RR difference, QT interval, and QT dispersion, did not correspond to the

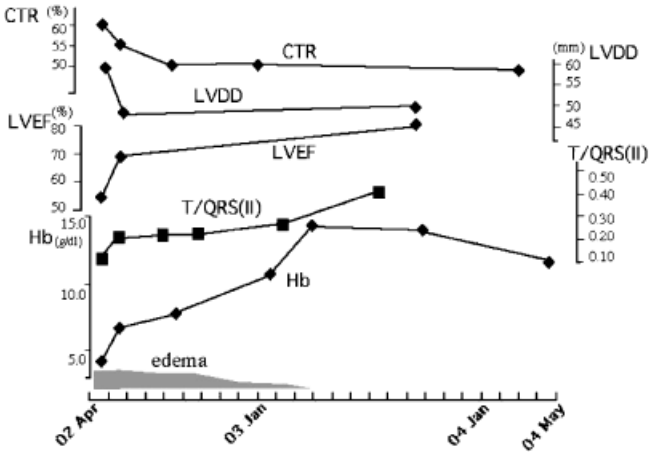

Figure 1. Cardiac function and hemoglobin (Hb) level. CTR = cardiothoracic ratio; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; T/QRS(II) = T-wave amplitude/QRS complex amplitude in lead II of the electrocardiogram.

improving cardiac function, the observed recovery of T-amplitude revealed a good correlation with that of cardiothoracic ratio, left ventricular ejection fraction, and left ventricular dilatation at diastolic phase (Figure 1). This observation implies that the T/QRS ratio is a good indicator of cardiac malfunction caused by severe chronic anemia. Accumulation of further evidence is necessary to confirm the correlation between T-amplitude and cardiac dysfunction in chronic severe anemia.

In the present case, prolonged pretibial edema was observed even at 10 g/dL of Hb after a prompt recovery of cardiac function. This implies that pretibial edema in older patients caused by cardiac malfunction with severe anemia is prone to persist and that the edema can be erased by raising Hb to more than 11 g/dL. In cases of anemia in older patients, low T-wave and a cardiothoracic ratio greater than 50% may be a hint of the presence of anemia. Although 12g/dL of Hb is the limit value of WHO criteria in women, 11 g/dL can be regarded as a candidate value for the goal of treatment of anemia to keep sufficient cardiac function even in cases aged 85 and older.

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