Original Paper

Eur Neural 1997;37:225-229

Received: June 10, 1996

Accepted: November 7, 1996

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Hypovitaminosis D and Decreased Bone Mineral Density in Amyotrophic Lateral Sclerosis

Key Words

Amyotrophic lateral sclerosis
Bone mineral density
Vitamin-D deficiency
Hyperparathyroidism

Abstract

To assess the bone health of patients with amyotrophic lateral sclerosis (ALS), we evaluated the bone density and serum biochemical indices of bone metabolism in 11 ALS patients. The serum concentration of 25-hydroxyvitamin D (25-OHD) was significantly lower in patients (14.0 ± 3.7 ng/ml) than in controls (25.2 ± 4.0 ng/ml), at deficient levels (< 10 ng/ml) in 2, and at insufficient levels (10-20 ng/ml) in 9 patients. Serum levels of parathyroid hormone (PTH) and ionized calcium were elevated in 8 and 6 patients, respectively. Dietary intake of vitamin D was below the recommended level (100 IU) in 10 patients, and 10 patients were in a sunlight-deprived state. The metacarpal bone density (MBD) and the metacarpal index (MCI) of the second metacarpal bone were measured by computed X-ray densitometry. Z scores of the MBD and the MCI were negative in 7 and 6 patients, respectively. The serum concentration of 25-OHD was positively correlated with the Z score of the MBD ($p < 0.05$, $r = 0.727$) and negatively with the PTH level ($p < 0.05$, $r = -0.410$). The degree of dysfunction of hand grip also correlated with the Z score of the MBD ($p < 0.05$, $r = 0.749$). These data underscore the importance of hypovitaminosis D and compensatory hyperparathyroidism in the development of osteopenia in patients with ALS.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disease of the central nervous system characterized by the progressive loss of motor neurons in the cortex, brain-stem, and spinal cord. A particular form of familial ALS has been linked to dominantly inherited mutations in the superoxide-dismutase-1 gene encoding Cu, Zn superoxide dismutase [1]. Moreover, the importance of glutamate in the pathogenesis of sporadic ALS has been supported by the findings of elevated glutamate levels in the serum, cerebrospinal fluid, and brain of patients with ALS [2, 3]. Clinical trials with riluzole, a drug that interferes with glutamatergic neurotransmission, show that survival of ALS patients is extended by 12% [4]. With the recent advances in therapeutic agents and the potential for prolonged survival, hypovitaminosis D may become a clinically relevant problem affecting the

quality of life of ALS patients. The main causes of the deficiency of vitamin D in these patients are thought to be sunlight deprivation in home-

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Table 1. Clinical information, biochemical indices and bone changes

1	71/F	
2	58/F	2
3	56/F	1
4	71/F	1
5	73/F	1
6	82/F	1
7	73/F	1
8	71/M	
9	60/M	1
1	57/M	2
1	73/M	2

Case
Normal range Patients¹ (n = 11) Controls¹ (n = 28)

	Duration of illness months	ALS rating scale	Hand grip kg	% IBW	25-OHD ng/ml	1,25-[OH] ₂ D pg/ml	Calcium total mg/dl	ionized mEq/l	Intact PTH pg/ml	MBD (Z score) mm Al	MCI (Z score)
71/F	4	45	5	91	12.2	24.9	9.6	2.52	15	1.65 (-1.6)	0.456(1.3)
58/F	24	112	6	68	8.8	38.5	9.5	2.50	32	1.38 (-4.1)	0.342 (-3.2)
56/F	15	60	7	65	19.7	42.0	9.4	2.60	50	2.43 (-0.5)	0.545 (0.8)
71/F	12	42	14	96	14.8	40.5	9.7	2.48	25	2.15(0.5)	0.415(0.1)
73/F	12	96	8	65	12.4	30.7	9.8	2.75	92	2.00(0.3)	0.367 (-0.8)
82/F	17	78	8	79	19.3	39.9	8.5	2.48	32	2.07 (0.8)	0.400 (0.3)
73/F	15	109	0	69	11.3	25.8	9.1	2.74	39	1.11 (-3.4)	0.244 (-4.0)
71/M	8	66	7	75	9.8	18.2	9.0	2.80	52	2.09 (-2.6)	0.436 (-0.1)
60/M	18	96	4	68	12.3	28.9	8.3	2.72	54	2.47 (-1.1)	0.432 (-0.4)
57/M	21	51	17	82	14.9	36.3	9.3	2.60	45	2.88(0.4)	0.466 (0)
73/M	27	45	7	75	18.1	45.6	8.3	2.48	21	2.25 (-1.8)	0.411 (-0.6)
Normal range				<80	21- 29	43- 71	8.8-10.2	2.356-2.524	17- 31		
Patients ¹ (n = 11)		73±27		76±10	14.3± 3.7	33.8 + 8.6*	9.1	2.6±0.13*	41.5±21.2**		
Controls ¹ (n = 28)					25.2 + 4.0	57.4± 14.0	9.5+0.7	2.44 + 0.08	24.3± 7.0		

p<0.001, ** not significant. 1,25-[OH]₂D= 1,25-Dihydroxyvitamin D. Values are mean ± SD.

bound patients and in patients with prolonged periods of hospitalization, and decreases in dietary intake mainly due to bulbar palsy. Consequently, the patients are at increased risk for osteoporosis [5-7]. In addition to hypovitaminosis D, immobilization is another important cause of osteoporosis [8, 9]. To assess the bone health in ALS, we measured the bone density and biochemical indices of bone metabolism in 11 ALS patients.

Patients and Methods

Eleven patients (4 men and 7 women, with ages ranging from 56 to 82 years, a mean of 67.7 ± 8.5), who were manifesting signs of progressive muscular weakness and atrophy with evidence of both upper and lower motor neuron disease and no significant sensory loss, were enrolled in this study. Patients receiving artificial nutrition were excluded from the study. In 8 of the 11 patients, bulbar involvement was obvious. The duration of illness ranged from 4 to 27 months, with an average of 15.7 ± 6.8 months. Eight outpatients were homebound, and 3 hospitalized patients were nonambulatory.

Patients completed a questionnaire concerning diet and sunlight exposure. Mean weekly dietary vitamin-D intake was calculated for each individual.

According to the ALS rating scale of Appel et al. [10], swallowing and speech abilities, respiratory function, and both strength and function of upper and lower extremity musculature were scored. A score of 30 points indicates normal motor function; 164 points indicate maximal dysfunction. In addition, patient weight was expressed as percentage of ideal body weight (%IBW). IBW was calculated based on each patient's height and body frame using the Metropolitan Life Insurance table. Values below 70% of IBW represent severe wasting and those below 60% represent extreme wasting.

Using a computed X-ray densitometer (Teijin Limited, Tokyo) [11, 12], the metacarpal bone density (MBD) and the metacarpal index (MCI) of the second metacarpal bone were measured on the left or right hand, depending on the handedness of the patient unless the degree of hand grip dysfunction was lateralized. The standard deviation (SD) for the normal control in each gender and age group was used to calculate the Z score. A total of 28 age-matched (66.3 ± 5.8 years) volunteers (12 males and 16 females) served as controls.

On the same day as the bone evaluation, blood samples were obtained in the fasting state. Blood was drawn from patients and controls. Serum samples were analyzed for total calcium, ionized calcium, parathyroid hormone (PTH; 1-84; intact PTH), 25-hydroxyvitamin D (25-OHD), and 1,25-dihydroxyvitamin D. Serum ionized calcium was measured under anaerobic conditions using an ionized-calcium analyzer (Nova Biochemical, Newton, Mass., USA) with an ion-selective electrode. Intact PTH was measured by a radioimmunoassay method (Allegro intact PTH, Nichols Institute Diagnostics, San Juan Capistrano, Calif., USA). Serum 25-OHD was determined using a competitive protein-binding assay, and 1,25-dihydroxyvitamin D was determined by a radioreceptor assay using calf thymus receptor (Nichols Institute Diagnostics).

A serum 25-OHD concentration of less than 10 ng/ml was considered deficient, a concentration of between 10 and 20 ng/ml was categorized as insufficient, and a concentration of greater than 20 ng/ml was considered sufficient on the basis of previously reported Japanese data [13]. Serial determinations of bone changes and biochemical indices were performed in 4 patients. Normal ranges of the biochemical indices were determined based on the values obtained from the controls (mean ± 1 SD, table 1).

All patients and volunteers were informed of the nature of the study; consent was obtained from each participant in the presence of a witness. The protocol of the study was approved by the Human Investigation Committee at the Futase Social Insurance Hospital.

226
Eur J Neurol 1997;37:225-229
Sato/Honda/Asoh/Kikuyama/Oizumi
Table 2. Serial determination of biochemical indices and bone changes

Case										
Duration ALS of illness rating months scale										
Hand										
grip										
kg										
25-OHD Calcium										
ng/ml	t^aI	mg/dl								
ionized mEq/l										
Intact PTH	MBD (Z score)	MCI (Z score)								
pg/ml	mm Al									
2.	24	112	6	13.8	9.5	2.50	32	1.38(- -4.1)	0.342 (- -3.2)	
	30	121	5	13.9	9.3	2.48	48	1.46(- -3.7)	0.322 (- -3.8)	
	33	153	1	8.7	9.2	2.52	65	1.51(- -4.0)	0.336(- -3.5)	
3.	15	60	6	19.7	9.4	2.60	50	2.43 (- -0.5)	0.545 (0.8)	
	21	72	5	15.0	9.3	2.72	58	1.98(- -2.0)	0.540 (0.3)	
	33	157	0	9.8	9.0	2.90	80	2.44 (- -3.0)	0.549 (0.9)	
9.	18	96	4	12.3	8.3	2.72	54	2.47 (- -1.1)	0.432 (-0.4)	
	30	144	0	11.0	8.8	2.77	76	2.08 (- -2.7)	0.357 (- -1.5)	
11	27	45	7	18.1	8.3	2.48	21	2.25(- 1.8)	0.411(- -0.6)	

39	75	3	20.3	8.6	2.52	35	2.08 (- 2.6)	0.406 (- -0.7)
45	102	0	8.9	8.0	2.68	97	2.05 (- -3.2)	0.405 (- -0.7)
Case numbers			correspond to those in table 1.					

Data are presented as mean ± SD. Biochemical indices were compared using the unpaired t test. To compare each serum index of bone metabolism, hand grip, ALS rating scale and Z scores, Spearman’s rank correlation coefficients were calculated. Values of p less than 0.05 were considered to be statistically significant.

Results

Clinical Characteristics and Serum Indices of Bone Metabolism

The clinical characteristics, serum biochemical indices, bone density, ALS rating score, and hand grip strength of the patient population and controls are summarized in table 1. Values below 70% of IBW were observed in 5 patients. Two (cases 2 and 3) out of 5 patients who had bulbar palsy and were severely debilitated received intravenous infusion of 500-1,000 ml of 5% glucose for 2 months before their deaths. The remaining 9 patients did not receive any artificial nutrition including feeding by a percutaneous endoscopic gastrostomy because they or their family members refused such therapy. The concentration of serum 25-OHD was significantly lower in patients than in controls, with deficient values (less than 10 ng/ml) in 2 patients and insufficient values (10-20 ng/ml) in 9 patients. The serum levels of PTH and those of ionized calcium were elevated in 8 and 6 patients, respectively, exceeding the upper limits of the normal ranges, 32 pg/ml for the former and 2.524 mEq/l for the latter. This increase in PTH and ionized calcium was significant compared to the control group. Conversely, in 3 patients the serum level of total calcium was below the lower limit, 8.6 mg/dl.

Interrelationship between Biochemistry and Bone Density

Z scores of MBD and MCI were negative in 7 and 6 of the 11 patients, respectively. The serum 25-OHD concentration correlated positively with the Z score of the MBD (p < 0.05, r = 0.727) and negatively with the PTH level (p < 0.05, r = -0.410). Likewise, the score for the hand grip was positively correlated with the Z score of the MBD (p < 0.05, r = 0.749). The ALS rating scale was positively correlated with the serum level of ionized calcium (p < 0.05, r = 0.675).

Serial Determination

The results of serial determinations of the bone density and the biochemical indices over the course of development in 4 patients with ALS are summarized in table 2. As the disease progressed, serum levels of 25-OHD were decreased, whereas both PTH and ionized calcium levels were increased in all 4 patients. Serum level of total calcium was decreased in 1 patient. Z scores of both the MBD and the MCI were unchanged in 1 patient (case 2), whereas they declined in another patient (case 9). In the remaining 2 patients (cases 3 and 11), only the Z score of the MBD declined, while the Z score of the MCI was unchanged.

The intake of vitamin D was below the Japanese recommended daily allowance (100 IU) in 10 patients. Also, all patients except for 1 (case 11) were in a sunlight-deprived state because they were homebound or in prolonged periods of hospitalization.

Discussion

Our data suggest that disturbances in calcium metabolism occur in a considerable proportion of patients with ALS. That abnormalities in calcium regulation should exist in patients with progressive neuromuscular disorders is not surprising. Reduced bone mass with vitamin-D deficiency and compensatory hyperparathyroidism are well-recognized in patients with multiple sclerosis [7] and Binswanger's syndrome [Sato et al., unpubl. data]. A negative calcium balance manifest by a decrease in the size of the miscible calcium pool, a decreased rate of bone formation accompanied by an increased rate of bone resorption, and a decrease in the percentage of cortical area of the second metacarpal bone has already been demonstrated in patients with ALS [14]. A reduction in radiologically detectable cortical bone in the second metacarpal, correlating with muscle atrophy and weakness, has been previously demonstrated in 8 Chamorros with ALS [15]. Moreover, approximately one half of these patients had hypovitaminosis D, reduced intestinal calcium absorption, hypocalcemia in terms of both ionized and nonion-ized calcium, and an associated increase in the serum intact PTH [15]. Mallette et al. [16] likewise have found mild hypocalcemia in terms of both ionized and nonion-ized calcium, and elevation of the serum intact PTH level in 2 of 12 patients with ALS. In both of these patients, the plasma 25-OHD concentration was at normal or lowered levels and the intestinal calcium absorption was reduced.

Serum sampling was distributed equally across all four seasons of the year. No substantial seasonal fluctuation in the serum 25-OHD level was observed, although seasonal fluctuation in vitamin-D levels has been reported [17]. Since serum 25-OHD is derived from dietary intake and is produced in the skin by sunlight, its concentration is a function of endogenous and exogenous factors [18, 19]. Serum 25-OHD, the most abundant circulating metabolite [20], has been shown to be the most sensitive and generally useful index of the vitamin supply. Our dietary survey reveals a dietary vitamin-D intake that is less than 100 IU (the Japanese recommended daily allowance level) in 10 patients. Although sunlight exposure normally can compensate for even minimal dietary intakes of vitamin D [21], 10 patients had sunlight deprivation. In fact, many ALS patients are homebound or have restrictions in their activity which limit sunlight exposure.

Our data indicated that all 11 patients with ALS had vitamin-D deficiency, likely due to both sunlight deprivation and decreased dietary intake as evidenced by the dietary survey and that in all of them the serum levels of calcium, in terms of total calcium, remained within or changed to below the normal range. In contrast, the serum PTH level was elevated in 8 patients and was negatively correlated with the 25-OHD level. It has been reported that accelerated bone resorption occurs in an immobilized state and results in osteoporosis [22]. Therefore, hypercalcemia in terms of ionized calcium in ALS patients may be a reflection of the accelerated bone resorption caused by immobilization, as evidenced by a positive correlation between the ALS rating scale and the serum level of ionized calcium. These biochemical abnormalities became more evident in 4 patients as the disease progressed. These data suggest that vitamin-D deficiency and compensatory hyperparathyroidism, in addition to muscular weakness, were the primary contributors to the bone density

deficiency seen in these patients with ALS. A close correlation was demonstrated between the Z score of the MBD and the serum vitamin D and the degree of dysfunction of hand grip. In 2 patients, serial Z scores of the MBD declined, while those of the MCI remained unchanged in 2 patients. These data indicate that ALS is characterized by a loss of bone mineral content rather than of bone mass.

As stated above, vitamin-D deficiency with compensatory secondary hyperparathyroidism and immobility causes may be decisive factors contributing to bone density loss in the second metacarpal in patients with ALS. An apparent association between low levels of 25-OHD with compensatory hyperparathyroidism and a decrease in bone mineral density has been demonstrated in multiple-sclerosis patients [7], immobilized stroke patients [Sato et al., unpubl. data], and in elderly nursing-home patients [23]. Therefore it seems unlikely that the abnormalities and changes in bone metabolism are specific for ALS patients. However, in light of the results of the present study and studies by others [4], we should aim at establishing strategies for the extension of survival of ALS patients. One such strategy may be the use of vitamin-D supplementation to correct vitamin-D deficiency in patients with ALS. A prospective trial of vitamin-D supplementation to prevent the progression in biochemical indices and radiographic assay of bone loss in ALS patients would be necessary.

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