

Risk Factors for Fracture in Adult Patients with Cerebral Palsy

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Most studies on risk factors for fracture in patients with cerebral palsy have been conducted in children. We examined the relationships between age, body mass, gender, osteoporosis, osteomalacia and mobility level with history of a previous fracture in adult patients with cerebral palsy. We studied 124 institutionalized adults (52 men, age: 21-56 years, and 72 women, age: 24-47 years) with cerebral palsy. Antero-posterior radiographs of the pelvis were examined for osteoporosis and graded using the Singh index. Serum calcium, phosphate and alkaline phosphatase were measured. Osteoporosis was defined as grade 1-4 in Singh index. Osteomalacia was defined as calcium < 8.6 mg/dl, phosphate < 2.5 mg/dl or alkaline phosphatase > 220 U/l. Body mass index (BMI) was calculated from body height and weight. Medical records were examined for history of previous fractures and mobility levels (ambulatory /non-ambulatory). A history of previous fracture was noted in 17 patients (6 men and 11 women). The proportion of osteoporosis in non-ambulatory patients was higher than in ambulatory patients. Multiple logistic regression analysis showed that presence of osteoporosis and mobility level (ambulation) were two factors that significantly correlated with a history of fracture. The latter did not correlate with age, BMI, gender and osteomalacia. Our findings suggest that osteoporosis is an important risk factor for fracture in adults with cerebral palsy. Since falling is also a risk factor for certain fractures, fractures seem to be more likely to occur in ambulatory patients through falling despite the low prevalence of osteoporosis.

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Introduction

Children who are severely affected with cerebral palsy often have stunted growth, osteopenia, and develop frequent fractures [1-7]. Several studies have shown that children with cerebral palsy have a tendency to sustain fractures, which are often related to osteoporosis, osteomalacia, contractures, immobility and poor nutrition [6, 8, 9]. However, there are only a few studies on the potential risk factors of bone fractures in adults with cerebral palsy [6]. In the present study, we focused on adults with cerebral palsy and analyzed the relationships between history of fracture with age, body mass, gender, osteoporosis, osteomalacia and mobility levels.

Patients and Methods

Subjects and analyzed parameters

We studied 124 institutionalized adults (52 men aged 21-56 years and 72 pre-menopausal women aged 24-47 years) with cerebral palsy defined as severe physical handicap and mental retardation due to cerebral injuries sustained during fetal development or perinatally. Antero-posterior radiographs of the pelvis were obtained and graded for osteoporosis according to the Singh index [10], and osteoporosis was defined as grade 1-4. Radiographs of four men were not obtained due to hip contracture. Radiographs were classified by one investigator (T.A.) who was blinded to the clinical information. Serum concentrations of calcium, phosphate and alkaline phosphatase were measured by standard laboratory methods. In this study, osteomalacia was defined as hypocalcemia (calcium <8.6 mg/dl), hypophosphatemia (phosphate <2.5 mg/dl), or elevated alkaline phosphatase (alkaline phosphatase >220 U/l) [11, 12]. Height (m) and weight (kg) were measured with the patient in light clothing and without shoes, and body mass index (BMI) was calculated as weight (kg)/height (m²). The medical

records were examined for history of fracture, mobility levels (ambulatory/non-ambulatory) and anticonvulsant use. Unfortunately, the accurate site, reason and time occurred of fracture were not available in every case in the current study. However, all cases had fractures due to minor or moderate trauma within 5 years.

Statistical analysis

Differences in proportions between groups were examined for statistical significance using the chi-square test. Multiple logistic regression analysis was used to explore the relationship between previous fracture and age, BMI, gender, osteoporosis, osteomalacia and mobility level. Data were analyzed using SAS software (SAS Institute, Cary, NC, USA).

Results

Characteristics of patients are shown in Table 1. Six percent of men and 15% of women had hypocalcemia. None of the men and 1.4% of women had hypophosphatemia. Thirty-nine percent of men and 25% of women had elevated alkaline phosphatase levels. Thirty-eight percent of men and 36% of women had osteomalacia. Half of men and about one third of women had osteoporosis. Approximately half of the patients (63.5% in men and 40.3% in women) received anticonvulsant treatment.

A total of 17 patients (6 men and 11 women) had history of a previous fracture. Table 2 shows the proportion of these fractures according to the presence or

Table 1. Patients characteristics.

	Men			Women		
	Mean	SD	Range	Mean	SD	Range
Age	32.0	5.6	21-56	33.3	4.8	24-47
Height (cm)	148.8	10.7	126-172	142.6	9.3	125-164
Weight (kg)	36.1	7.4	20.0-59.0	36.5	6.5	24.5-53.0
BMI ^a (kg/m ²)	16.3	2.5	10.6-20.5	18.0	2.8	11.7-27.5
Serum						
calcium (mg/dl)	9.2	0.5	7.5-10.1	9.0	0.4	8.1-10.0
phosphate (mg/dl)	3.7	0.5	2.7-5.5	3.6	0.5	2.4-5.0
ALP ^b (U/l)	216	96	70-472	190	106	59-479
	No.	%		No.	%	
Hypocalcemia (<8.6 mg/dl)	3/52	5.8		11/72	15.3	
Hypophosphatemia (<2.5 mg/dl)	0/52	0.0		1/72	1.4	
Elevated ALP ^b (>220 U/l)	20/52	38.5		18/72	25.0	
Osteomalacia ^c	20/52	38.4		26/72	36.1	
Osteoporosis ^d	24/48	50.0		21/72	29.2	
Anticonvulsant use	33/52	63.5		29/72	40.3	

a : body mass index.

b: alkaline phosphatase.

c: Osteomalacia was defined as serum calcium <8.6 mg/dl, phosphate <2.5 mg/dl or alkaline phosphatase >220 U/l.

d: Osteoporosis was defined as grade 1-4 by the Singh index.

Table 2. Proportion of patients with a previous fracture by osteoporosis, osteomalacia status, and mobility levels.

	Men			Women		
	n	%	P	n	%	P
Osteoporosis*						
Yes	3/24	12.5	0.64	6/21	28.6	0.04
No	2/24	8.3		5/51	9.8	
Osteomalacia						
Yes	4/20	20.0	0.13	4/26	15.4	0.99
No	2/32	6.3		7/46	15.2	
Mobility level						
Non-ambulatory	4/40	10.0	0.52	7/54	13.0	0.34
Ambulatory	2/12	16.7		4/18	22.2	

See Table 1 for definition of osteoporosis and osteomalacia.

* Radiographs of four men were not obtained due to hip contracture.

absence of osteoporosis, osteomalacia, and mobility level. The proportion of fractures in men with osteoporosis was not different from that in men without osteoporosis. In contrast, the proportion of fractures in women with osteoporosis was significantly higher than in women without osteoporosis. In both men and women, history of a previous fracture did not differ between the presence and absence of osteomalacia, or between the mobility levels (Table 2).

Further analysis showed that the prevalence of osteoporosis in non-ambulatory patients was higher than in ambulatory patients. Osteoporosis was noted in 59% (22/37) of men who were non-ambulatory, but in only 18% (2/11) of men who were ambulatory. Similarly, osteoporosis was noted in 39% (21/54) of women who were non-ambulatory, but in none (0/18) of women who were ambulatory. The proportion of anticonvulsant use in osteomalacia was 95% (19/20) in men and 73% (19/26) in women (data not shown).

Multiple logistic regression analysis showed that presence of osteoporosis and mobility level (ambulation) were two parameters that significantly correlated with a history of previous fracture (Table 3). The same analysis showed that age, BMI, gender and osteomalacia did not correlate with a history of previous fracture.

Table 3. Odds ratios and 95% confidence intervals of a previous fracture in multiple logistic regression analysis.

	Unit	Odds ratio	95% confidence interval
Age	10 years increase	0.5	0.1-1.9
Body mass index	5 kg increase	1.1	0.4-3.1
Gender	women/men	2.6	0.7-9.2
Osteoporosis	yes/no	6.5	1.4-29.1
Osteomalacia	yes/no	1.1	0.3-3.3
Mobility levels	ambulatory/ non-ambulatory	5.8	1.2-26.9

See Table 1 for definition of osteoporosis and osteomalacia.

Discussion

A recent consensus conference defined osteoporosis as a metabolic bone disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility with a consequent increase in fracture risk [13]. Several studies reported that osteoporosis-related fractures represent a major problem in severely handicapped children and young adults [6, 7]. In the present study, half of men and about one third of women had osteoporosis, and our multiple logistic regression analysis showed that the presence of osteoporosis was significantly associated with a history of a previous fracture, confirming the results of previous studies [6, 7].

Although the proportion of a fracture history in women with osteoporosis was higher than that in women without osteoporosis, the proportion in men with osteoporosis was not different from that in men without osteoporosis. The reason of this finding is not clear. Our diagnosis of osteoporosis was conducted using radiographs of pelvis, and the severity was not considered in the current study, which may influence the results.

Our results showed that patients who were non-ambulatory were more likely to have osteoporosis than ambulatory patients. Immobility is a significant risk factor for bone loss and osteoporosis [14]. Studies on the effect of long-term bed rest in healthy volunteers demonstrated significant bone loss [15, 16]. Furthermore, several studies in children with cerebral palsy showed that the ambulation was associated with higher bone mineral density [1-3]. Although the physical capacity of patients with cerebral palsy may be greatly restricted, they could conceivably benefit from even a minimal program of weight-bearing activity [17, 18]. It should be the therapeutic goal of health professionals to promote active standing and other forms of weight-bearing activities to reduce potential bone loss and susceptibility to fracture in these patients.

Multiple logistic regression model in our study revealed that ambulation, associated with less frequent osteoporosis, was significantly associated with a previous fracture history. Although low bone mass or osteoporosis is one important risk factor for bone fractures [19], there is evidence to suggest that bone fracture cannot always be explained by low bone mass [20, 21]. For example, Japanese have lower bone mass than Caucasians [22, 23], but Japanese have a lower incidence of hip and other nonspine fractures than Caucasians [24, 25]. Hip fractures usually occur after a fall, and differing incidence rates of falls might

explain the observed differences in hip fracture rates [26]. Based on the above findings and the present results, we suggest that patients who are ambulatory are more likely to fall, compared with non-ambulatory patients, and hence, prevention of falling is important, and protection against fractures is recommended in these patients.

Several studies have shown that anticonvulsant agents can alter bone metabolism and predispose to the development of osteomalacia, thus enhancing the likelihood of fracture occurrence [7, 27]. Although approximately half of our patients were on anticonvulsant therapy, osteomalacia (defined based on serum levels of calcium, phosphate and alkaline phosphatase) was not associated with a history of previous fracture. Since we did not examine the amount of osteoid in bone biopsy, the definition of osteomalacia used in our study may be divergent diagnosis or low specificity of diagnosis. In addition, we did not measure the bone specific alkaline phosphatase, and information on liver function was not available in the current study. Furthermore, since osteomalacia is a disease characterized by relative deficiency of minerals relative to collagen, which distinguishes it from osteoporosis (normal mineral/collagen ratio), both osteoporosis and osteomalacia show low bone minerals in radiographs. Thus, our cases identified as having osteoporosis based on visual analysis of their radiographs may include those with osteomalacia or osteoporomalacia.

We compared the body size of our patients with those of Japanese sample examined in National Nutrition Survey, Japan [28]. The estimated values of height, weight and BMI in the Japanese sample among aged 30-39 years were 170.8cm, 66.6kg and 22.8kg/m² in men, and 157.3cm, 54.0kg and 21.8kg/m² in women, respectively. Our patients had shorter height, lighter weight and leanness, compared with the Japanese sample examined in National Nutrition Survey, Japan. Oral-motor dysfunction can make feeding difficult for many individuals with cerebral palsy [29], and poor nutrition is common in this population [4, 5]. Low calcium and vitamin D intake associated with poor nutrition could contribute to the development of osteoporosis [1].

Patients with cerebral palsy tend to develop contractures [8, 9]. Some patients may have increased tone in certain groups of muscles and involuntary extensor spasms. However, information on contractures was not available in the present study.

In conclusion, we have demonstrated in the present study that osteoporosis is not uncommon in adult patients with cerebral palsy, and that the presence of osteoporosis was significantly associated with a history

of previous fracture among adult patients with cerebral palsy. Our findings suggest that osteoporosis is an important risk factor for fracture in adults with cerebral palsy. Furthermore, falling also seems to be a risk factor for some fractures [20, 21]. Our results also suggest that fractures is more likely to occur in ambulatory patients through falling despite the low probability of osteoporosis. It is necessary to prevent fractures through reduction of risk of both osteoporosis-related and fall-related factors among adult patients with cerebral palsy.

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References

- Henderson RC, Lin PP, Greene WB: Bone-mineral density in children and adolescents who have spastic cerebral palsy. *J Bone Joint Surg Am* 77: 1671-1681, 1995
- Wilmshurst S, Ward K, Adams JE, et al: Mobility status and bone density in cerebral palsy. *Arch Dis Child* 75: 164-165, 1996
- Tasdemir HA, Buyukavci M, Akcay F, et al: Bone mineral density in children with cerebral palsy. *Pediatr Int* 43: 157-160, 2001
- Stallings VA, Charney EB, Davies JC, et al: Nutrition-related growth failure of children with quadriplegic cerebral palsy. *Dev Med Child Neurol* 35: 126-138, 1993
- Stallings VA, Charney EB, Davies JC, et al: Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. *Dev Med Child Neurol* 35: 997-1006, 1993
- Lee JJ, Lyne ED: Pathologic fractures in severely handicapped children and young adults. *J Pediatr Orthop* 10: 497-500, 1990
- Nilsson OS, Lindholm TS, Elmstedt E, et al: Fracture incidence and bone disease in epileptics receiving long-term anticonvulsant drug treatment. *Arch Orthop Trauma Surg* 105: 146-149, 1986
- Lingam S, Joester J: Spontaneous fractures in children and adolescents with cerebral palsy. *BMJ* 309: 265, 1994
- Brunner R, Doderlein L: Pathological fractures in patients with cerebral palsy. *J Pediatr Orthop B* 5: 232-238, 1996
- Singh M, Nagrath AR, Maini PS: Changes in trabecular pattern of the upper end of the femur as an index of osteoporosis. *J Bone Joint Surg Am* 52: 457-467, 1970
- Nippon Rinsho; Kohani ketsueki nyuu kagaku kensa menekigakuteki kensa (Japanese). (Nippon Rinsho Sha, Tokyo) 1995
- Klein GL. Nutritional rickets and osteomalacia. In: *Primer on the metabolic bone diseases and disorders of mineral metabolism* (Favus MJ eds.; Lippincott Williams & Wilkins, Philadelphia) pp. 315-319, 1999
- Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 94: 646-650, 1993
- Ross PD: Osteoporosis. Frequency, consequences, and risk factors. *Arch Intern Med* 156: 1399-1411, 1996
- Donaldson CL, Hulley SB, Vogel JM, et al: Effect of prolonged bed rest on bone mineral. *Metabolism* 19: 1071-1084, 1970
- Leblanc AD, Schneider VS, Evans HJ, et al: Bone mineral loss and recovery after 17 weeks of bed rest. *J Bone Miner Res* 5: 843-850, 1990
- Stuberg WA: Considerations related to weight-bearing programs in children with developmental disabilities. *Phys Ther* 72: 35-40, 1992
- Chad KE, Bailey DA, McKay HA, et al: The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. *J Pediatr* 135: 115-117, 1999
- Cummings SR, Black DM, Nevitt MC, et al: Bone density at various sites for prediction of hip fractures. *Lancet* 341: 72-75, 1993
- Cummings SR, Nevitt MC, Browner WS, et al: Risk factors for hip fracture in white women. *N Engl J Med* 332: 767-773, 1995
- Dargent-Molina P, Favier F, Grandjean H, et al: Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 348: 145-149, 1996
- Norimatsu H, Mori S, Uesato T, et al: Bone mineral density of the spine and proximal femur in normal and osteoporotic subjects in Japan. *Bone Miner* 5: 213-222, 1989
- Kin K, Lee JH, Kushida K, et al: Bone density and body composition on the Pacific rim: a comparison between Japan-born and U.S.-born Japanese-American women. *J Bone Miner Res* 8: 861-869, 1993
- Hagino H, Yamamoto K, Ohshiro H, et al: Changing incidence of hip, distal radius, and proximal humerus fractures in Tottori Prefecture, Japan. *Bone* 24: 265-270, 1999
- Ross PD, Norimatsu H, Davis JW, et al: A comparison of hip fracture incidence among native Japanese, Japanese Americans, and American Caucasians. *Am J Epidemiol* 133: 801-809, 1991
- Aoyagi K, Ross PD, Davis JW, et al: Falls among community-dwelling elderly in Japan. *J Bone Miner Res* 13: 1468-1474, 1998
- Tolman KG, Jubiz W, Sannella JJ, et al: Osteomalacia associated with anticonvulsant drug therapy in mentally retarded children. *Pediatrics* 56: 45-50, 1975
- Japanese Ministry of Health and Welfare: Kokumin-Eiyo-no-Genjo (Nation's Nutritional Status). (Dai-ichi-Shuppan, Tokyo) 1999
- Reilly S, Skuse D: Characteristics and management of feeding problems of young children with cerebral palsy. *Dev Med Child Neurol* 34: 379-388, 1992