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Risk factors of long bone fracture in non-ambulatory cerebral palsy children

臥床的大腦癱瘓症兒童長骨骨折的風險因素

Objectives. To identify the risk factors for long bone fractures in non-ambulatory cerebral palsy children.
Design. Case-control study.
Setting. A residential rehabilitation centre in Hong Kong.
Patients. The fracture group comprised 19 (13 male, 6 female) cerebral palsy children aged 4 years 5 months to 18 years 11 months (mean, 10 years; standard deviation, 3 years 9 months), who had their first long bone fracture during the period June 1992 to May 2001 inclusive. The control group was composed of 90 (46 male, 44 female) concomitant cerebral palsy residents aged 6 years 1 month to 16 years 11 months (mean, 9 years 11 months; standard deviation, 2 years 4 months) with no history of long bone fracture.
Main outcome measures. Presence of features considered relevant to the risk of fracture, namely: anthropometry, feeding practice, orthopaedic surgery and duration of postoperative immobilisation, extremity contracture, anti-epileptic medications, and general health status in the 12 months prior to the fracture.
Results. Of the 19 fracture episodes, 18 occurred in the femur and one in the tibia/fibula. Multivariate analysis revealed that weight for age Z scores (adjusted odds ratio=0.41, 95% confidence interval, 0.19-0.86) and recent postoperative immobilisation (weeks) [adjusted odds ratio=1.35, 95% confidence interval, 0.97-1.89] were independent predictors for fracture occurrence.
Conclusion. Early intervention targeting these risk factors may reduce the fracture risk in non-ambulatory cerebral palsy children.

目的：找出臥床的大腦癱瘓症兒童，其長骨骨折的風險因素。
設計：病例對照研究。
安排：香港一間住院式復康中心。
患者：骨折組包括1992年6月至2001年5月期間，首次發生長骨骨折的大腦癱瘓症兒童，共19人（13男，6女），年齡介乎4歲5個月至18歲個11月（平均年齡：10歲；標準差：3年9個月）。對照組則為與骨折組一同住院而沒有骨折病歷的大腦癱瘓症兒童，共90人（46男，44女），年齡介乎6歲1個月至16歲11個月（平均年齡：9歲11個月；標準差：2年4個月）。
主要結果測量：研究與骨折風險因素有關的資料，包括：人體測量學資料、病人飲食習慣、有否接受矯形外科手術、手術後臥床的時間、有否肢體攣縮、有否使用抗癲癇藥，以及骨折前12個月的一般健康狀況。
結果：在19宗骨折事件中，18宗發生在大腿骨，1宗在脛骨／腓骨。多變量分析顯示，年齡與體重關係的標準分數（Z scores）（經調整風險比率=0.41，95%置信區間，0.19-0.86）和近期的手術後臥床的時間（以星期計算）（經調整風險比率=1.35，95%置信區間，0.97-1.89）為兩項獨立的骨折風險因素。
結論：針對這些風險因素的治療，可減少臥床的大腦癱瘓症兒童長骨骨折的可能。

Key words:
Cerebral palsy;
Fractures, bone;
Immobilization

關鍵詞：
大腦癱瘓症；
骨折；
臥床

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Introduction

Long bone fracture is a common problem in non-ambulatory cerebral palsy (CP) children. Up to 20% sustain a femoral fracture during their lifetime.[1] Henderson et al[2] found that increasingly severe neurological impairment, difficulty in feeding, use of anti-convulsants, and lower triceps skinfold thickness contribute to lowering bone mineral density (BMD) Z scores in the distal femur. However, BMD is only an indirect indicator of the fracture risk. In fact, a low spinal BMD was not predictive of fracture.[3] Moreover, routine measurement of axial

and appendicular BMD is not feasible in CP patients with multiple contractures.[2]

This case-control study set out to identify the clinical predictors for the first fracture of a long bone in a group of institutionalised non-ambulatory CP children. Instead of using BMD as an indirect indicator of fracture risk, we used the fracture incident as a direct outcome measure. We particularly focused on the following clinical variables: nutritional status, feeding practice, orthopaedic surgery, neuromuscular status, anti-epileptic drug (AED) usage, and general health status. It was anticipated that recommendations to reduce the risk of fracture in the future could be generated after determining clinically significant risk factors.

Methods

Patients

The Developmental Disabilities Unit (DDU) of Caritas Medical Centre is the largest residential unit for severe mentally retarded children in Hong Kong. Among its 200 inhabitants, over 50% have CP. The fracture group was composed of all CP children residing in the DDU who had their first fracture of a long bone between June 1992 and May 2001 inclusive. If a patient had multiple episodes of fracture, only the data related to the first episode were collected. This eliminated the confounding effect of previous fractures—a risk factor for developing subsequent fractures.[3] Patients with traumatic fractures and pathological fractures predisposing to diseases (including chronic renal failure and osteogenesis imperfecta) were also excluded. The data recorded included the age, sex, type of CP (spastic, dyskinetic, or mixed), cause of mental retardation (if any), date and site of fracture, anthropometry, feeding practice, orthopaedic surgery, duration of postoperative immobilisation, extremity contracture, AED use, and general health status in the 12 months preceding the fracture.

Controls

The control group comprised CP children residing in the DDU, without a history of long bone fracture within the defined period. It is difficult to decide which year of a control subject's lifetime should be extracted for the corresponding data. The subjects were first divided into two groups by duration in the residence: <5 years and ≥5 years. Each group was further divided into four age-groups: <9 years, 9 to <12, 12 to <15, and ≥15 according to their ages in July 2001. Each fracture patient was then matched with controls of similar age and duration in the residence. For each control, corresponding data were extracted with reference to the date of the first fracture of the matched patient in the fracture group.

Anthropometry

It was a routine practice in the DDU to measure every patient's weight at least every 3 months. For patients with nutritional problems, their body weights were measured monthly. The body weights at 6 and 12 months before the fracture were recorded and the corresponding percentage changes computed. Contracture, inability to stand and scoliosis sometimes meant that it was not feasible to measure the standing height of these children. Therefore, instead of estimating the weight for height, weight for age (at the time of fracture) was determined, and Z scores were calculated based on references data from a 1993 territory-wide growth survey in Hong Kong children.[4]

Feeding practice

The predominant route of feeding (oral or tube/gastrostomy) at the time of fracture was recorded. The usual type and amount of oral feeds (ordinary, blended, fine blended, congee, or milk) within the last 6 months was also recorded. An oral feeder who was estimated to complete over 70% of most meals by the respective caretaker was graded as satisfactory; otherwise feeding was graded as poor. This cut-off value served as a general guideline for the caretaker to be alerted to malnutrition from poor intake. For any child with persistently unsatisfactory oral intake, body weight was closely monitored and the dietician or doctor was notified to make an assessment.

Orthopaedic surgery and postoperative immobilisation

The number and types of operations, the duration of post-surgery immobilisation, and any associated complications ensuing in the 12 months preceding the fracture, were recorded.

Musculoskeletal status

The number of children who regularly undertook weight-bearing exercise for at least 4 hours per day was recorded. Ambulatory children were also recorded as weight-bearers. At the time of fracture, the presence of major large joint fixed contractures in any extremity noted by orthopaedic surgeons during their regular ward rounds was recorded. Major contractures were defined as those resulting in reduced active and passive range of motion of the affected joint, or those that prohibited assessment of the underlying spasticity.[5]

Anti-epileptic medications

Over 75% of DDU patients taking anti-convulsants received valproate.[6] The use of valproate was reviewed in detail, including the maximum dosage within 3 months of the index fracture, and the dosage per kg body weight.

Pulmonary condition

The pulmonary status was defined as poor if in the period of 12 months prior to the fracture, there was a history of mechanical ventilation, or two or more episodes of chest infection.

Statistical analysis

Statistical Package for the Social Sciences for Windows version 9.0 (SPSS Inc., Chicago [IL], US) was used for data

Table 1. Demographic data

Demographic data	Fracture group (n=19)	Control group (n=90)
Mean age (SD) [years]	10 (3.8)	10 (2.3)
Sex		
Females	6	44
Males	13	46
Cerebral palsy		
Spastic	15	62
Mixed spastic/dyskinetic	4	28
Cause of mental retardation		
Asphyxia	7	23
Prematurity	1	5
Infections	5	14
Cerebral malformations	2	4
Syndromal	0	3
Degenerative	0	1
Miscellaneous	1	15
Unknown	3	25
Sites of fracture		
Femur	18	-
Tibia/fibula	1	-

analysis. In univariate analysis, parametric and non-parametric continuous data were analysed by independent sample *t*-tests and Mann-Whitney *U* tests, respectively. Categorical data were compared by Chi squared and Fisher's exact tests. In the second phase of any of the following analysis, covariates approaching statistical significance in the univariate analysis were entered by multifactorial stepwise regression. The following covariates were included in the multivariate analysis: predominantly oral feeding, difficulty in feeding by caretaker, operations on bone within 12 months, presence of extremity contractures, and use of anti-convulsants. A logistic regression model was fitted to assess the independent predictors of fracture. Statistical significance was defined as a two-tailed probability below 0.05.

Results

Demographic data

The fracture group consisted of 19 children (6 females and 13 males). The mean age when the fracture occurred was 10 years (standard deviation [SD], 3 years 9 months). Eighteen fractures occurred in the femur and one in the proximal tibia and fibula. The control group was composed of 90 children (44 females and 46 males); according to the data extracted, their mean age was 9 years 11 months (SD, 2 years 4 months) [Table 1].

The child with the proximal tibia and fibula fracture was a 6-year-old boy with birth asphyxia, resulting in profound mental retardation, hydrocephalus, epilepsy, and spastic tetraplegia. At the age of 4 years, he underwent right hip derotation and varus osteotomy for dislocation. He remained non-ambulatory and was placed in a moulded seat during daytime. He was an oral feeder with no major feeding problem. The weight for age Z score was -2.14 at the time of fracture. He was taking valproic acid 400 mg per day for seizure control. The fracture occurred at age 6 and presented as swelling and pain over the right knee and shin. There was no major manipulation prior to the incident. X-ray confirmed fracture of the right tibia and fibula with minimal displacement. It healed 4 weeks after closed reduction and plaster slab immobilisation.

Univariate analyses

Anthropometry

The weight for age Z score of the fracture group was significantly lower than that in the controls (P=0.01). No significant differences were found with respect to percent changes in body weight from 6 months (P=0.29) and 12 months (P=0.44) before the date of the index fracture (Table 2).

Feeding practice

Three (16%) of the 19 children with fractures were tube feeders, while 22 (24%) in the controls received tube feeding (P=0.55). Among the oral feeders, no significant difference was found with respect to difficulty of feeding as reported by the caretakers (P=0.24) [Table 2].

Orthopaedic surgery

There was no significant difference between the two groups in the number of orthopaedic operations (soft tissue plus bone surgery) undertaken within the defined 12-month period (P=0.12), and even if only bone surgery alone was considered (P=0.21). However, the corresponding total duration of postoperative immobilisation was significantly longer in the fracture group than in the controls (mean±SE: 6.63±3.09 vs 1.94±0.48 weeks; P=0.04) [Table 2].

Musculoskeletal status

Most of the children in both groups did not bear weight throughout the day. There was no significant difference in the proportions of extremity contractures reported (P=0.42) [Table 2].

Anti-epileptic medications

The number of children receiving AEDs in both groups was similar (P=0.44). Likewise, in the subgroup analysis during the defined 3-month antecedent periods, maximal daily dosage and the dose/kg body weight were comparable (P=0.21 and 0.48) [Table 2].

Pulmonary status

Seven (37%) of the patients from the fracture group and 28 (31%) of the controls were reported to have a chronically poor pulmonary status (P=0.60).

Multivariate analysis

In the univariate analyses, a lower weight for age Z score and prolonged postoperative immobilisation within the prior 12 months were significantly associated with the occurrence of fracture. When the covariates (see Methods) were analysed by logistic regression, weight for age Z score (adjusted odds ratio [OR]=0.41; 95% confidence interval

Table 2. Univariate analyses of potential predictors of fracture

Variables	Fracture group (n=19)	Control group (n=90)	P value
Anthropometry			
Mean % change of weight in 6 months (SE)	2.37 (1.97)	4.50 (0.80)	0.29
Mean % change of weight in 12 months (SE)	10.08 (3.16)	7.87 (1.10)	0.44
Mean weight for age Z score (SE)	-2.41 (0.20)	-1.93 (0.07)	0.01
Feeding practice			
Tube	3	22	0.55
Oral	16	68	
Oral feeding*			
Unsatisfactory	2	3	0.24
Satisfactory	14	65	
Orthopaedic surgery in the past 12 months†			
Yes	5	12	0.17
No	14	78	
Bone surgery			
Yes	2	3	0.21
No	17	87	
Mean immobilisation period (SE) [weeks]	6.63 (3.09)	1.94 (0.48)	0.04
Weight bearing			
Yes	0	2	1.00
No	19	88	
Contractures			
Yes	8	28	0.42
No	11	62	
Anti-epileptic medications			
Yes	13	50	0.44
No	6	40	
Valproate			
Yes	9	39	0.80
No	10	51	
Mean dose/day (SE) [mg]	384 (97)	537 (56)	0.21
Mean dose/kg (SE) [mg]	24 (6)	29 (3)	0.48
Pulmonary status			
Poor	7	28	0.60
Satisfactory	12	62	

* Satisfactory denotes >70% of meals finished
† Including all soft tissue and bone surgery

[CI], 0.19-0.86) and weeks of immobilisation (adjusted OR=1.35; 95% CI, 0.97-1.89) remained significant independent predictors for fracture (goodness of fit=112.275; R^2=0.175) [Table 3].

Table 3. Multivariate analysis of potential predictors of fracture

Covariates	Adjusted OR	95% CI	P value
Weight for age Z score	0.41	0.19-0.86	0.02
Immobilisation (weeks)	1.35	0.97-1.89	0.08
Non-tube feeding	-	-	0.78
Poor oral feeder	-	-	0.99
Bone surgery	-	-	0.46
Contracture	-	-	0.17
Anti-epileptic drugs	-	-	0.14

Discussion

Malnutrition is a common problem in CP children. In a population-based sample of 235 children with moderate and severe CP, 47% had a weight below the fifth percentile; one third had estimated mid-upper arm fat and muscle areas below 10th percentile.[7] In an assessment of body composition (based on the deuterium oxide dilution method) in 28 prepubertal spastic quadriplegic children, both fat mass and fat-free mass were significantly lower than in normal controls.[8] However, research on the effects of malnutrition in CP is lacking. Anecdotal reports suggest it may result in inadequate linear growth, increased surgical morbidity, delayed decubitus ulcer healing, and increased mortality.[9-12] Given the importance of parental views on oral feeding and the fear of potential complications from gastrostomy feeding, the latter is often regarded as a last resort for nutritional therapy. This delay in treatment may also be perpetuated by the lack of objective reference data on 'normal' nutritional status, and caretakers fearing that their charges might become 'overweight'.[7] In the present study, we have demonstrated a significant association between lower weight for age Z scores and fracture in non-ambulatory CP children. The identification of this negative effect (presumably from malnutrition) provides important evidence for family counselling on nutritional rehabilitation.

In CP, pathological femoral fracture is common after hip surgery. Two retrospective studies revealed that up to one third of non-ambulatory CP patients developed femoral fractures within a few months after hip osteotomies, whilst the risk was significantly lower in ambulatory children.[1,13]

The underlying mechanism has been attributed to multiple factors, including: long and fragile lever arms, joint stiffness, prolonged postoperative spica casting, and co-morbidities such as from gastrostomy and tracheostomy.[1,3,13] The individual contribution from each of these interrelated factors remains unknown. Our findings implicate prolonged postoperative immobilisation as an important independent risk factor, even after adjustment for the nature of the operation, ambulatory status, and preoperative nutritional status. The risk appears to increase approximately 1.3 fold per week of immobilisation after surgery. Possibly, prolonged immobilisation results in significant mineral loss and aggravates any pre-existing osteoporosis[1,3,13] in such non-ambulatory children.[14]

We could not demonstrate any association of AED with increased fracture rate in our non-ambulatory CP children. Early studies suggested that treatment with phenytoin, primidone, and phenobarbitone may induce catabolism of 25-hydroxyvitamin D, resulting in biochemical and radiological rickets.[15-18] A more recent study also revealed that AED use was associated with reduction in total body BMD in adults, and that the effect was more marked in those taking enzyme-inducing AEDs (eg carbamazepine, phenytoin, phenobarbital).[19] In ambulatory children with uncomplicated epilepsy, valproate therapy was associated with a 10 to 14% reduction in BMD,[20,21] yet this effect has not been consistently demonstrated.[22] A prospective cohort study is needed to investigate the effect of AEDs on the fracture risk of non-ambulatory CP children.

To lower the incidence of fracture, a proactive approach is needed to target these potential risk factors. Regular nutritional assessment is necessary to identify malnourished children. Gastrostomy tube placement should be considered early in their nutritional rehabilitation programme. For oral feeders, vitamin D and calcium supplementation should be considered in those who cannot consistently finish most of their meals. Supplementation is particularly important in patients for whom major orthopaedic operations that prolonged immobilisation are being contemplated. Recent advances in tone reduction procedures (including selective dorsal rhizotomy, continuous intrathecal baclofen infusion, and botulinum toxin injection) may help to alleviate the hypertonicity, prevent contracture development, and decrease the need of orthopaedic intervention. Pilot studies have demonstrated that bisphosphonates augment BMD in paediatric CP patients.[23] A recent retrospective review of the use of intravenous pamidronate in 18 CP children revealed a significant increase in BMD (in excess of the age-specific growth) and there was no fracture after the first week of treatment.[24] Allington et al[25] administered cyclic intravenous pamidronate to 18 osteoporotic (Z score <2.5) non-ambulatory children with CP or a neuromuscular disorder. One year after treatment, there was improvement in bone densitometry, decrease in pain on manipulation, and no new fractures. Nonetheless, a prospective controlled study with longer follow-up is required to investigate the long-term effectiveness of such drugs in preventing fracture. We suggest further clinical trials to focus on children with the aforementioned adverse factors.

Conclusion

In non-ambulatory spastic or dyskinetic CP children with no prior history of fracture, a low weight for age Z score and prolonged postoperative immobilisation were found to be significant independent risk factors predictive of pathological fracture. Identification of these factors is important for planning future preventive measures.

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