Fractures in children with cerebral palsy: a total population study

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AIM To analyse factors associated with fractures in children with cerebral palsy (CP) in different levels of Gross Motor Function Classification System (GMFCS).

METHOD This was an epidemiological retrospective study of a total population of 536 children (214 females, 322 males) with CP born between 1990 and 2005. CP type was unilateral spastic (n=159), bilateral spastic (n=225), ataxic (n=60), dyskinetic (n=80), and mixed type (n=12); 384 children were in Gross Motor Function Classification Scale (GMFCS) levels I–III and 152 children were in GMFCS levels IV–V. Data were collected for a 9-year period on sex, CP-type, GMFCS level, gastrostomy, height, weight, the use of a standing device, antiepileptic drug (AED) therapy, and fractures.

RESULTS The risk of fracture in the total population of children with CP was similar to that for typically developing children. The risk for fractures of those in GMFCS levels I–III was not significantly associated with any of the studied risk factors. The risk of fractures for those in GMFCS levels IV–V on AED therapy was a twofold increase (p=0.004). The risk for fractures without trauma in children with stunted growth (height for age <−3 SD) and those who did not use standing devices was significantly increased: adjusted incidence rate ratio (AIRR) 4.16 (p=0.011) and 3.66 (p=0.010) respectively. Results regarding gastrostomy feeding for those in GMFCS levels IV–V were conflicting: a gastrostomy was associated with a reduced risk of fractures with trauma, but with increased risk of fractures without trauma (AIRR 0.10, p=0.003 and 4.36, p=0.012) respectively.

INTERPRETATION Children in GMFCS levels I–III had a similar incidence and pattern for fractures as normally developing children. Those in GMFCS levels IV–V had stunted growth, often a sign of longstanding undernourishment, and were associated with an increased risk of fractures. Children using standing devices had a fourfold reduction of fractures without trauma. Regular loading exercises and early adequate nutritional intake could prevent fractures in severe CP.

It is well known that fractures constitute a common clinical problem in children with CP, especially in conjunction with an inability to walk. Stevenson et al.[1] reported on 62 fractures in 46 children with moderate to severe CP. They determined that low bone mineral density (BMD) was prevalent in children with moderate to severe CP and this was associated with a significant increased risk of fractures. The increased risk was associated with higher body fat, having a gastrostomy, and earlier fractures. Henderson et al.[2] also measured BMD in children with moderate to severe CP and concluded that low BMD was common in children with moderate to severe CP and was associated with a significant increased risk of fractures. In a later study, Henderson et al.[3] associated low BMD with low weight, non-ambulatory status, feeding difficulties, history of previous fractures, and the use of antiepileptic drugs (AEDs). Young ambulatory children with good growth and nutritional status, as indicated by normal weight for age, were in the subset more likely to have normal BMD. Henderson et al.,[4] in a prospective study, assessed the natural history of growth in BMD in children and adolescents with moderate to severe CP. They reported that, during the course of their life, the rate of mineralization diminished compared with the rate in healthy children. Osteopenia could therefore be viewed as a manifestation of growth failure. Poor nutrition contributes to diminished growth. A retrospective study[5] correlated low BMD of the distal femur and low body mass index (BMI) with the occurrence of fragility fractures and concluded that these factors may relate to increased fracture risk. The greatest risk factors for fracture in all children were being non-ambulatory and taking AEDs.

Mergler et al.[6] concluded in a review that there was only a limited amount of high quality evidence on low BMD

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and fractures in children with severe CP. They associated the increased risk of low BMD with limited ambulation, feeding difficulties, previous fractures, use of AEDs, and lower fat mass. Earlier studies have focused on BMD and the risk of fractures in CP. No previous study has determined the risk of fractures in a cohort of children with CP or studied a total population of children with CP and the risk of fracture with regard to GMFCS level, and the risk in typically developing children.

The objectives of this study were (1) to determine factors that were associated with the incidence of fractures in all children and adolescents with CP, independent of CP subtype and GMFCS level; (2) to determine localization and type of fracture and the possible risk factors involved: age, sex, GMFCS level, CP subtype, gastrostomy feeding, BMI, height-for-age, the use of AEDs, and use of standing devices; (3) to do a descriptive analysis of fractures without trauma and possible risk factors; and (4) to compare the incidence of fractures among children and adolescents with CP with the incidence in typically developing children. The study was approved by the local medical research ethics committee and Lund University (LU-443-99).

METHOD

Study design

This was an epidemiological total population study with prospectively collected data on body function, activity, and treatment in a CP follow-up registry, including retrospective information on fracture events and radiographic findings.

Definitions

CP was defined according to the criteria described by Rosenbaum et al.[7] CP subtype was determined after the fourth birthday, according to the Surveillance of Cerebral Palsy in Europe protocol.[8] Gross motor function was classified according to the GMFCS, which is an age-related five-level classification in which level I represents the least and level V the most functional limitation.[9] The GMFCS level used was the one most recently reported by the child's local physiotherapist, who used the recently extended version of the classification (GMFCS Expanded and Revised).[10] Epilepsy was defined as having had at least two unprovoked seizures after the neonatal period. All the children with a diagnosis of epilepsy were treated with AEDs. Indication for a gastrostomy was dysphagia and other severe eating problems with poor weight gain. The date of the onset of epilepsy and the introduction of gastrostomy feeding were obtained in order to be able to relate the risk of fracture to the amount of years with epilepsy and enteral feeding respectively. Thinness was defined as a BMI of less than −2SD, obesity as greater than 2SD, and children with stunted growth as height-for-age of less than −3SD. Trauma was categorized into four groups: fractures without any known trauma; slight trauma (corresponding to a fall from <0.5m); moderate trauma; (0.5–3m) and severe trauma (>3m).

What this paper adds

- Children in GMFCS levels I–III had a similar incidence and pattern for fractures as typically developing children.
- For children in GMFCS levels IV–V stunted growth status was associated with increased fracture risk.
- Epilepsy was present in all children with fractures without trauma.
- Regular use of standing devices was associated with a reduced risk of fractures without trauma.

Participants

In 1994,[11] a health care programme for children with CP, coupled with a CP registry, known as CPUP, was initiated in Skåne, Sweden, a county with a population of 1.25 million. A systematic search to find all children with CP and to offer them a chance to participate in CPUP was performed in 1998, 2002, 2006, and 2010.[12] The Skåne CPUP programme includes continuous standardized follow-up, including the monitoring of comorbidities in CP.

In this retrospective cohort study, the inclusion criteria were children and young adults with CP born 1990 to 2005, participating in the CPUP programme and living in Skåne during the whole or part of the study period including dates for moving in and out of the area. Data collected in the CPUP database from 1 January 2002 to 31 December 2010 were used. Data on epilepsy and gastrostomy feeding were analysed only in children with severe functional limitations (GMFCS IV–V). Data on children in GMFCS levels I–III were analysed separately from those in GMFCS levels IV–V. Fractures were searched for using Kundrad, a radiological electronic system for radiographic referral notes and radiologist results that have existed in Skåne from 2002.

Statistical analysis

Three outcomes were examined in the present study: (1) the incidence of all fractures as well as incidence of fractures with and without trauma; (2) the influence of factors such as age, sex, GMFCS level, type of CP, age, gastrostomy feeding, BMI, height-for-age; and (3) the use of AEDs and standing devices on the different types of fracture incidence were evaluated using Poisson regression. The factors of having a gastrostomy and taking AEDs were considered to be time-dependent. In the analysis this was handled by dividing the follow-up time for each individual into 5-year age groups and using dichotomous variables to indicate whether the child had a gastrostomy and/or took AEDs during a specific 5-year interval. Analyses were performed for each factor separately as well as by multiple regression analysis including all variables in order to evaluate possible confounding factors. Results were expressed as incidence rate ratios (IRR) and adjusted incidence rate ratios (AIRR).

Comparison of the fracture incidence rate in the CP population to that of the general population was made using indirect standardization by sex and age (5y age groups) to calculate a standardized incidence ratio (SIR). The information on fracture incidence rates in the general population was collected from Tiderius et al.[13] Ninety-five

Table I: Characteristics of children in the study sample

Characteristic	GMFCS levels I–III (%)	GMFCS levels IV–V (%)	All (%)	Missing information
Number of children	384	152	536	
Sex				
Female	151 (39)	63 (41)	214 (40)	0
Male	233 (61)	89 (59)	322 (60)	
CP subtype				
Bilateral spastic	159 (41)	66 (44)	225 (42)	0
Unilateral spastic	157 (41)	2 (1)	159 (30)	
Ataxic	49 (13)	11 (7)	60 (11)	
Dyskinetic	15 (4)	65 (43)	80 (15)	
Mixed	4 (1)	8 (5)	12 (2)	
GMFCS level				
I	232 (43)	–	232 (43)	0
II	102 (19)	–	102 (19)	
III	50 (9)	–	50 (9)	
IV	–	82 (15)	82 (15)	
V	–	70 (13)	70 (13)	
BMI				
Within ±2SD	313 (85)	111 (72)	422 (79)	12
Thin (BMI <−2SD)	24 (6)	37 (24)	61 (11)	
Obese (BMI >2SD)	35 (9)	6 (4)	41 (8)	
Height				
≥ −3SD	356 (96)	105 (69)	461 (86)	13
Stunted growth (<−3SD)	16 (4)	46 (31)	62 (12)	
Fractures status				
No fracture	323 (84)	134 (88)	457 (85)	0
Fracture	61 (16)	18 (12)	79 (15)	
Children with >1 fracture	10 (3)	3 (2)	13 (2)	0
Standing devices				
No	–	27 (18)	N/A	0
Yes	–	125 (82)	N/A	
Gastrostomy				
No gastrostomy	–	87 (57)	N/A	0
Gastrostomy	–	65 (43)	N/A	
Epilepsy				
No epilepsy	–	55 (36)	N/A	0
Epilepsy	–	97 (64)	N/A	

GMFCS, Gross Motor Function Classification System; CP, cerebral palsy; BMI, body mass index; N/A, not applicable.

per cent confidence intervals (95% CI) and *p*-values for all two-sided tests of rate ratios and the SIR was calculated using Poisson analysis using STATA software, version 12 (StataCorp LP, College Station, TX, USA).

RESULTS

Of the total child population, 548 children were born between 1990 and 2005 and followed by in the CPUP program. Of these, 12 were excluded because they did not fulfil the criteria for a CP diagnosis, leaving 536: 214 females and 322 males. Eleven per cent were thin (BMI <−2 SD), 8% were obese (BMI >2SD) and 12% had a height below less than −3 SD. There were 103 fractures in 79 children and 13 children had more than one fracture.

The group with the most severe motor function limitations (GMFCS IV–V) consisted of 152 children (18%). In this selected group, 31% had stunted growth, 24% were thin, and 4% were obese. The vast majority used standing devices (82%), which meant that almost one-fifth did not. The majority of the children in GMFCS levels IV–V had epilepsy (64%) and 43% had a gastrostomy (Table I).

Table II: All fractures in relation to CP subtype and GMFCS (without trauma)

CP subtype	Fractures	GMFCS level	Fractures
Bilateral spastic	37 (10)	I	42 (0)
Unilateral spastic	28 (0)	II	20 (1)
Ataxic	15 (0)	III	10 (1)
Dyskinetic	10 (3)	IV	17 (4)
Mixed type	13 (6)	V	14 (13)
	103		103

CP, cerebral palsy; GMFCS, Gross Motor Function Classification System.

In total, 103 fractures were recorded: 19 (18%) occurred without any known trauma, 2 (2%) were in children in GMFCS levels I–III and 17 (16%) in children in GMFCS levels IV–V; 56 (54%) occurred after slight and 28 (27%) after moderate trauma. No fracture after severe trauma was found. Fractures without trauma occurred once in children

Table III: Analysis of factors associated with fractures in children with cerebral palsy

	Incidence rate ratio (range), *p*	Adjusted incidence rate ratio (range), *p*
GMFCS levels I–III		
Factors associated with fractures after slight or moderate trauma		
Thin	0.97 (0.35–2.66), 0.950	0.97 (0.34–2.77), 0.961
Obese	0.58 (0.21–1.59), 0.290	0.60 (0.21–1.62), 0.302
Stunted	0.71 (0.17–2.91), 0.638	0.75 (0.18–3.22), 0.704
Factors associated with fractures without trauma		
Thin	_[a]	_[a]
Obese	8.84 (0.55–141.3), 0.123	_[a]
Stunted	_[a]	_[a]
GMFCS levels IV–V		
Factors associated with fractures after slight or moderate trauma		
Thin	0.41 (0.09–1.78), 0.233	0.24 (0.05–1.10), 0.066
Obese	1.45 (0.19–10.94), 0.721	0.44 (0.06–3.51), 0.441
Stunted	2.64 (0.98–7.09), 0.054	4.80 (1.75–13.2), 0.002
Not using standing device	0.30 (0.04–2.31), 0.250	0.36 (0.05–2.86), 0.334
Gastrostomy	0.24 (0.05–1.05), 0.059	0.10 (0.02–0.47), 0.003
Epilepsy	2.82 (0.80–9.91), 0.105	5.61 (1.54–20.5), 0.009
Factors associated with fractures without trauma		
Thin	0.87 (0.28–2.68), 0.813	0.53 (0.16–1.74), 0.295
Stunted	4.93 (1.74–14.0), 0.003	4.16 (1.40–12.4), 0.011
Not using standing device	3.20 (1.22–8.41), 0.018	3.66 (1.37–9.82), 0.010
Gastrostomy	5.45 (1.78–16.7), 0.003	4.36 (1.39–13.7), 0.012
Epilepsy	_[b]	_[b]

[a]Not possible to analyse, because of small sample. [b]Not possible to analyse, since all children in Gross Motor Function Classification (GMFCS) levels IV–V with fractures without known trauma were treated for epilepsy.

in GMFCS levels II and III, four times in GMFCS level IV, and 13 times in GMFCS level V (Table II). In GMFCS level I, the most common fractures occurred in the distal forearm (12%) and fingers (10%), and in GMFCS levels IV–V in the femur (14%). Of the 15 fractures of the femur, 14 occurred in children in GMFCS levels IV–V, and in 11 of those cases there was no known trauma involved. The majority of fractures occurred in children in GMFCS level I, and the fractures without trauma were most common in children with spastic CP and those in GMFCS levels IV–V.

In GMFCS levels I–III there was no increased risk for fracture with or without trauma for any of the included risk factors, though there were too few cases to properly explore the factors associated with fracture without trauma. In GMFCS levels IV–V several factors were associated with a significantly increased risk of fracture (Table II); around a fivefold increased risk of fractures with slight or moderate trauma was present in children with stunted growth (AIRR 4.80; 1.75–13.2, p=0.002) and in children with epilepsy (AIRR 5.61; 1.54–20.5, p=0.009). Having a gastrostomy was associated with a significantly decreased risk for fractures after slight or moderate trauma (AIRR 0.10; 0.02–0.47, p=0.003). The risk for fracture without trauma in children with stunted growth and for those having a gastrostomy were both increased fourfold (AIRR 4.16; 1.40–12.4, p=0.011, and AIRR 4.36; 1.39–13.7, p=0.012). Not using a standing device was also associated with a significantly higher risk (AIRR 3.66; 1.37–9.82, p=0.010) (Table III). All the children with fracture without trauma were treated with AEDs, which meant that the AIRR could not be calculated. When the risk of all kinds of fractures was calculated for the whole group of AED-treated children in GMFCS levels IV–V, the IRR was 1.91 (1.24–2.96, p=0.004).

In addition, the same analysis as above but also adjusted for sex and age was performed among the children in GMFCS levels I–III and IV–V. The results were almost identical to those that were not adjusted, though risk factors associated with fractures without trauma could not be calculated because there were too few cases.

The incidence for fracture in this study was compared with the incidence among children described by Tiderius et al.[13] The SIR for fractures was 12.5% (7.2–36.5%, p=0.231) higher in the population with CP than in the general child population. When fractures without trauma were excluded in the CP population the SIR dropped to 8.2% (13.7–25.9%, p=0.431) below the incidence in the general population. The fracture incidence for males compared with females with CP, adjusted for age and GMFCS level, was AIRR 1.02 (0.68–1.51, p=0.981). Comparing the incidence of fractures without trauma yielded an AIRR of 1.55 (0.59–4.09, p=0.374). Most fractures in all GMFCS groups occurred between 10 years and 14 years of age (Table IV). The median age for fractures with trauma in females was 10.4 years, and 12.2 years without trauma. In males, the figures were 10.8 and 11.2 respectively. Events of fractures and person-years distributed by GMFCS level, sex, and age are presented in Table IV.

DISCUSSION

Fractures constitute a common clinical problem for persons with CP according to earlier studies.[1,2] In this study we wanted to investigate if the risk of fractures among children and young people with CP, depending on GMFCS level, in a total population was increased com-

Table IV: Events of fracture (fracture without trauma) and number of person-years; distribution by GMFCS level, sex, and age

		All			Males			Females		
GMFCS level	Age	Fractures	Person-years	Incidence/1000	Fractures	Person-years	Incidence/1000	Fractures	Person-years	Incidence/1000
I–III	0–4	7 (1)	636.8	11.0 (5.2–23.1)	5 (0)	377.3	13.3 (5.5–39.2)	2 (1)	259.6	7.7 (1.9–30.8)
	5–9	24 (1)	1043.8	23.0 (15.4–34.3)	10 (1)	646.4	15.5 (8.3–28.8)	14 (0)	397.4	35.2 (20.9–59.5)
	10–14	33 (0)	1026.1	32.2 (22.9–45.2)	19 (0)	627.0	30.3 (19.3–47.5)	14 (0)	399.2	35.1 (20.8–59.2)
	15+	6 (0)	460.8	13.0 (5.9–29.0)	4 (0)	271.8	14.7 (5.5–39.2)	2 (0)	189.0	10.6 (2.6–42.3)
	Total	70 (2)	3167.5	22.1 (17.5–27.9)	38 (1)	1922.4	19.8 (14.4–27.2)	32 (1)	1245.1	25.7 (18.2–36.3)
IV–V	0–4	2 (0)	250.2	8.0 (2.0–32.0)	2 (0)	139.1	14.4 (3.6–57.5)	0 (0)	111.0	0
	5–9	10 (4)	405.8	24.6 (13.3–45.8)	7 (2)	217.5	32.2 (15.3–67.5)	3 (2)	188.3	15.9 (5.1–49.4)
	10–14	16 (10)	400.2	40.0 (24.5–65.3)	10 (7)	239.1	41.8 (22.5–77.7)	6 (3)	161.1	37.2 (16.7–82.9)
	15+	5 (3)	168.6	29.7 (12.3–71.2)	5 (3)	101.6	49.2 (20.5–118.3)	0 (0)	67.0	0
	Total	33 (17)	1224.8	26.9 (19.2–37.9)	24 (12)	697.3	34.4 (23.1–51.3)	9 (5)	527.5	17.1 (8.9–32.8)

GMFCS, Gross Motor Function Classification System.

pared with the risk in other children. This risk has not been investigated in any previous study.

There was no significant difference in the overall incidence of fractures among children with CP compared with children in the general population study.[13] The risk for males and females with CP was similar, in contrast to the results from the above mentioned study. In that study there was an increased risk in males, especially from the age of 13 when children tend to become more independent. In this study there was a higher incidence in both males and females at a younger age (median age approx. 11y). The same risk between the sexes could be due to the fact that males with CP have functional limitation in mobility and are less likely to engage in risk-related physical activities than typically developing males. None of the risk factors (being underweight, obese, or with stunted growth) was associated with a significantly higher risk for fractures in children in GMFCS levels I–III; given the fact that the kind of trauma and localization of fractures were similar to those in children without disabilities, this could mean that this group has about the same incidence and pattern as normally developing children, and differ very much from those in GMFCS levels IV–V.

Every other fracture in children in GMFCS levels IV–V occurred without trauma. Fracture of the femur was the most common in children in GMFCS levels IV–V and almost 80% of those occurred without trauma. There could have been an underestimation of fractures without trauma of two reasons: (1) an X-ray could have been obtained, but showed no evident signs of a fracture; (2) many of the children might not have been able to communicate pain with the consequence that no X-ray was obtained even though there was a fracture. There were no reported fractures of the vertebrae; either they had been missed or they did not exist in children and young adults despite the lower BMD. Henderson[14] in a study on 43 patients with spastic quadriplegia saw that the BMD fell with increasing age, though there was no increased risk of lumbar spine fractures despite very low spinal BMD.

In GMFCS levels IV–V there were several risk factors associated with fractures both with and without trauma. It is well known that epilepsy and AEDs have a negative impact on bone mineralization and, as a consequence, the risk of fractures can increase.[15–17] In the general population the risk is between two times and six times higher.[18,19] In this study AED therapy was associated with a significant twofold increase in fracture risk in GMFCS levels IV–V. Another risk factor could be a fall in conjunction with a seizure, though that was not the case with any of the children in this group. Older AEDs have been associated with rickets, but recently it has been established that newer drugs have also been associated with decreased bone mineral density.[15] Guo et al.[20] wrote that long-term use of valproate and lamotrigine was associated with short stature, low BMD, and reduced bone formation, but concluded that the effect was mediated through reduced physical activity rather than a direct link to the antiepileptic treatment. Sheth et al.[21] noticed a 10% reduction in BMD in children treated with valproate but not carbamazepine compared with controls. Most of the children in GMFCS levels IV–V and epilepsy in this study had been treated with several AEDs, valproate being the most common, followed by oxcarbazepine and lamotrigine.

Stunted growth was associated with a fourfold increased risk for fractures with and without trauma in GMFCS levels IV–V. Stunted growth could be due to the fact that the child had been undernourished from an early age. Even if the nutritional situation improved with age, maybe with the help of a gastrostomy, the chance of catching-up in height diminished for every year's delay. Having a gastrostomy was associated with a decreased risk of fracture with trauma to only a fourth, but with a fourfold increased risk for fractures without trauma, thus illustrating conflicting results. The role of a gastrostomy on the risk of fracture without trauma needs to be explored further. One cause might be that the majority of children in GMFCS levels IV–V with fractures without trauma in this study were 10 years or above and had been undernourished for a longer period before they received their gastrostomy. Another cause could be that the nutrition given through the gastrostomy is not sufficient for bone mineralization.

Peak bone mass develops in early childhood. Physical activity, particular intense activity with biomechanical loading is one of the most significant modifiable factors affecting

bone accrual in healthy children.[22–24] In a review, Karlsson et al.[25] summarized the results from numerous papers on physical exercise, physical activity, and BMD in healthy children and concluded that exercise during growth increased the peak bone mass and that moderate intensity exercise intervention programmes together with adequate nutrition are beneficial for skeletal development during growth. Long-term undernourishment increases the risk of lower bone density and could increase the risk of fracture with or without trauma. Adequate nutrition is an important factor known to influence bone accrual in children.[22] Obesity was not associated with increased risk for fractures as has been reported in previous studies.[1]

Children with CP in GMFCS levels IV–V lack weight bearing as a part of their everyday routine. Their impaired muscle function does not allow bones to be exposed to the mechanical forces needed for their optimal development and growth. Periods of immobilization due to illnesses and surgery further exacerbate this problem. In this study we showed an almost fourfold reduced risk of fracture without trauma in those children who had used standing devices on a regular basis. This supports the theory that regular loading exercises decrease the risk for fractures without trauma. In a randomized controlled study of a standing programme[26] it was shown that prolonged standing resulted in an improvement on vertebral bone mineral density but not on proximal tibiae; the femur was not tested. Chad et al.[27] in an 8-month programme of weight-bearing physical activity found an increased BMD in children with CP. Mechanical loading is important for improving bone strength, and regular daily use of standing devices should be advocated for all children who are unable to stand alone.[24] Prevention of severe contractures in the lower extremity is needed in order to maintain the ability to continue supported standing.

The focus of this paper has been to look at factors involved in the risk of fractures in children with CP. None of the studied risk factors was found to be significantly associated with an increased risk for fractures in children in GMFCS levels I–III and these children, in terms of incidence, type of fracture, and trauma involved, could be regarded as typically developing children. The factors associated with increased risk of fractures for those in GMFCS levels IV–V were epilepsy together with AEDs and stunted growth status, often a sign of longstanding undernourishment starting in early childhood. In fractures without trauma there was an additional risk for those who did not use standing devices, as well as in those who had a gastrostomy, indicating that these were the frailest of children. These associations indicate that using a standing device may protect against fracture without trauma and, together with early adequate nutritional intake, could be the best prevention of unnecessary fractures in children with severe CP.

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