Fracture Rates in Children with Cerebral Palsy: A Danish, Nationwide Register-Based Study

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Background: In children with cerebral palsy (CP), fracture rates have been reported to be higher than in the general population but age-specific fracture rates have not been directly compared and the effect of comorbid epilepsy needs elucidation. This impairs decision-making regarding bone health interventions.

Aim: We aimed to establish the age-specific fracture rates in children with CP with and without epilepsy in Denmark.

Materials and Methods: Data from Danish registers were combined to establish cohorts of children with and without CP born in Denmark from 1997 to 2007. Fracture rates were calculated for 1997–2016.

Results: We identified 1,451 children with CP and 787,159 without CP. Female/male fracture rates per 1,000 person-years were 23/27 with CP and 23/29 without CP. Male sex, epilepsy and anti-seizure medication, but not the diagnosis of CP or GMFCS-level, were associated with higher fracture rates. Relatively more lower extremity fractures occurred in non-ambulant children with CP.

Interpretation/Conclusion: We found no increased fracture rates in children with CP when compared to peers; however, fracture locations suggested bone fragility in non-ambulant children. All children with epilepsy and on anti-seizure medication had increased fracture rates. We suggest bone health optimization in these groups.

Keywords: fracture rate, cerebral palsy, children, Gross Motor Classification System, epilepsy, anti-seizure medication

Introduction

A fragility fracture is a severe complication for a child with cerebral palsy (CP), and some studies have reported fracture rates in children with CP to be more than doubled compared to peers without CP.1-3

Other studies reported only small differences.4,5 However, comparison in all publications has been indirect by comparing to historical and epidemiological data.

Fractures in children with CP typically occur in the lower extremities due to low-energy traumas associated with activities of daily living, thus being signs of bone fragility.6 Compared to children in the general population, children with CP have reduced bone accrual and a decreasing Bone Mineral Density (BMD) Z-score with increasing age.5 Low BMD as measured by dual x-ray absorptiometry (DXA) correlates with high fracture risk in adults7 and in children with CP.8,9 Another common comorbidity in CP patients is epilepsy, which has also been associated with fractures in general10 and specifically in children with CP.5 Epilepsy treatment with anti-seizure medication (ASM) has been associated with low BMD but the causal pathway remains debatable.6,11

In general, fracture surgery is performed to improve the functional results and the procedure may be complicated by low BMD. This implies that fractures in non-ambulant children with CP may most commonly be managed with...
conservative treatment as ambulation is limited and BMD often low. The management of bone health in children with CP depends to a large extent on the occurrence of fractures as this is the most direct and tangible symptom of poor bone health.\textsuperscript{12,13} Allocation of resources within a family or a healthcare system to improve bone health also depends on the size of the problem relative to other financial or time-consuming priorities. Thus, it is important to have solid information on fracture rates in children with CP and how these compare to children without CP.

Based on the above, we designed a large population-based study to examine yearly fracture rates in children with CP in comparison to the background population. We aimed to estimate fracture rates and describe the anatomical distribution of fractures in Danish children with CP compared to their peers. Further, to evaluate if non-surgical management was offered more frequently than surgical management. Finally, we investigate whether fracture rates in children with CP and epilepsy differed from the background population with and without epilepsy.

\textbf{Method}

\textbf{Study Design}

We conducted a national register-based study with up to 20 years follow-up using data from Danish medical databases to identify persons with and without CP born between 1997 and 2007. Linkage was accomplished through the unique ten-digit Civil Personal Register (CPR) number assigned by law to every resident in Denmark at birth or at the time of immigration. This study is reported following the STROBE extension RECORD guidelines.\textsuperscript{14}

\textbf{Study Population}

We established two cohorts: the CP cohort and the background cohort. The CP cohort consisted of all persons with CP born in 1997–2007 (both years 1997 and 2007 were included). The background cohort consisted of all persons without CP born in the same period.

\textbf{Data Sources and Variables}

Dates of birth or immigration and dates of death or emigration were identified in the Danish Civil Registration Database. The database contains daily updated personal information on all persons with a CPR number: name, address, birth registration, citizenship, church membership, parentage, vital status, marital status. The number of inhabitants without a social security number in Denmark is very low, and the data have high accuracy.\textsuperscript{15}

Persons with CP and their Gross Motor Function Classification System (GMFCS) levels were extracted from the National CP Registry (NCPR).\textsuperscript{17} In 2001 NCPR was validated to be 85\% complete, since then cross-reference with the Danish National Patient Registry was added to further improve completeness.\textsuperscript{16}

Dates of fractures and epilepsy diagnoses as well as surgery codes were extracted from the Danish National Patient Registry (DNPR), an administrative register established in 1977. Since 1995 all in- and out-patient contacts in secondary health care have been registered. Each healthcare contact is registered with the primary diagnosis, secondary diagnoses, administrative data, treatments, procedures and examinations. Diagnoses are coded according to the WHO’s 10th International Classification of Diseases. Surgical procedures are registered according to the NOMESCO Classification of Surgical Procedures.\textsuperscript{18}

Dates of redeemed ASMs by each individual during inclusion in the study were extracted from the Danish National Prescription Registry using specific Anatomical Therapeutic Chemical (ATC) codes as defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology.\textsuperscript{19} This registry contains individual-level data on all prescription medicines sold at Danish pharmacies since 1995.\textsuperscript{20} Prescription is required for all ASMs used for out-patient treatment in Denmark.

\textbf{Outcomes}

For each person in both cohorts, we searched for fractures diagnosed between 1997 and 2016. The date of a fracture was defined as the date of a healthcare contact containing a fracture diagnosis or a fracture surgery code. Healthcare contacts
containing a fracture diagnosis or a fracture surgery code for the following 120 days were not counted if the fracture had a similar location (eg, upper arm) to minimize counting post-fracture follow-up contacts as new fractures.

Sensitivity analyses were performed to explore the effect of grace periods of 90 days and 150 days after the occurrence of a fracture.

**Handling of Variables**

Age categories and GMFCS groupings were constructed with as many strata as possible without reporting values between one and five to avoid data protection violation due to reporting of small numbers. Ambulant children with CP were defined as GMFCS levels I–III, non-ambulant children with CP as GMFCS levels IV–V.

Epilepsy exposure time as a risk factor for fractures was defined as the time after the date of a person’s first epilepsy diagnosis (ICD-10 codes G40.0-G40.9).

Fracture surgery was defined as a healthcare contact containing a fracture surgery code.

ASM exposure time was defined to start at the time when a patient redeemed the first prescription for any ASM at a pharmacy. Exposure time ended three years after last redeemed prescription for any ASM as we expected bone quality recovery at this point. We excluded short-term treatment, where no further medicine was collected after the first six months because short treatment is unlikely to affect bone quality.

A full list of variables, data sources and methods of measurement is available in Supplementary Table 1.

**Statistical Methods**

We used SAS version 9.4 (SAS Institute, Cary, North Carolina) to perform data management and analyses. Throughout this paper, 95% confidence intervals (95% CI) were employed and fracture rates were expressed as fractures per 1000 person-years. To compare fracture occurrences, z-test with a 5% significance level was used. The fracture-free survivals in each cohort were compared using Log rank test. Fracture rates per year of age were calculated as the number of fractures registered to persons of the given age in the study population divided by the number of persons in the study population who were alive at their birthday of the given age.

Fractures in persons during ASM treatment were defined as fractures occurring during long-term ASM exposure as detailed above.

Fractures in persons with epilepsy were defined as fractures occurring during epilepsy exposure time as detailed above.

Missing data on date of birth or GMFCS level (CP cohort only) led to the exclusion of the person from the analysis.

We included children born in 1997–2007 as the National CP Registry covers all Danish regions for the birth years 1997 to 2007.16 Earlier years lack information on GMFCS-levels, and a new data-collection procedure was introduced for children born in 2008, involving the national follow-up program (CPOP).21

Follow-up started at birth and ended in 2016 due to a change in the National Patient Registry from version 2 to version 3 which affected registration of diagnoses in later years.

Persons were censored at death, emigration or the end of 2016. We did not censor persons who had limited periods within the study period with no registered address in Denmark. During these periods, these persons did not contribute with outcomes or follow-up time.

**Ethics**

The study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 603). Reporting of less than five outcomes was avoided due to data protection regulations. The authors of this study had no access to other parts of the databases used apart from the variables extracted. One of the authors (GR) was a pediatric neurologist responsible for entering clinical data into the National Cerebral Palsy Registry.
Results

We identified 1470 unique persons born 1997–2007 in the National CP Registry. Nineteen (1.3%) persons were excluded from the study: one lacked the CPR number in the National Patient Registry and eighteen were excluded due to missing GMFCS level. The remaining 1451 persons entered the CP cohort. Complete follow-up was available for 1328 persons, while 123 persons emigrated (20 persons) or died (103 persons) before the end of 2016.

Thirty-six percent of the children with CP were non-ambulant, and 36% were diagnosed with epilepsy during follow-up. The total follow-up time of the CP cohort was 20,499 person-years.

In the National Patient Registry, 788,629 persons were born in 1997–2007 (Greenland and Faroe Islands not included). We excluded the 1470 persons identified through the CP register as detailed above and included a total of 787,159 persons in the background cohort. The total follow-up time of the background cohort was 11,210,498 person-years.

The mean follow-up time was 14.1 and 14.2 years in the CP and the background cohort, respectively. See characteristics of the cohorts in Table 1.

A total of 1,425 persons (25 with CP) had limited periods within the study period with no registered address in Denmark. Each of these periods was at least 100 days and averaged 2.6 years per person. 518 fractures occurred in the CP cohort corresponding an overall fracture rate of 25.3 per 1,000 person-years (95% CI 23.1–27.5). Stratifying this result by walking ability, we observed 365 and 153 fractures in ambulant children with CP and non-ambulant children with CP, respectively. The resulting total fracture rates were 27.3 (95% CI 24.5–30.2) for ambulant children and 21.5 (95% CI 18.2–25.1) for non-ambulant children. In the background cohort 292,919 fractures were registered corresponding a fracture rate of 26.1 (95% CI 26.0–26.2).

To evaluate the timing of the first fracture in both cohorts, we created an overall comparison of the fracture-free survival including both genders as shown in Figure 1. Overall, ambulant children with CP followed the same fracture-free survival curve as the background cohort while non-ambulant children with CP had a higher fracture-free survival from around twelve years of age. Yet, no statistically significant difference was found between non-ambulant children and ambulant children with CP ($p=0.18$) or the background cohort ($p=0.16$).

As seen in Figure 2, age-specific fracture rates were lowest in small children while they rose in the age groups 5–9 and 10–14 years of age. A decline was seen in the 15–19-year-olds. From the age of 10–14, males with and without CP had significantly higher fracture rates than the females of the same group. This was evident in ambulant as well as in non-ambulant children with CP (see Figure 2 and Supplementary Table 2 for results stratified by gender, age and ambulation). In the background cohort, we found 40,351 fracture surgery codes, which correspond to 14% of the number of fractures in the cohort. In the CP cohort, we found 76 fracture surgery codes, which correspond to 15% of the fractures in the cohort. When this result was stratified by GMFCS level, we found 14% (n = 36) in GMFCS level I, 11% (n = 12) in GMFCS levels II–III, 13% (n = 7) in GMFCS level IV and 21% (n = 21) in GMFCS level V. GMFCS levels II and III were combined to avoid data protection violation by reporting low numbers. Thereby, the only

| Characteristics | Background Cohort | Cerebral Palsy Cohort |
|-----------------|-------------------|-----------------------|
|                 | GMFCS I–V         | GMFCS I               | GMFCS II–III   | GMFCS IV   | GMFCS V   |
| Total n         | 787,159           | 1451                  | 668           | 254        | 218        | 311        |
| Male / female (% of total n) | 51% / 49% | 59% / 41% | 58% / 42% | 66% / 34% | 56% / 44% | 58% / 42% |
| Epilepsy‡§, n (% of total n) | 8725 (1.1%) | 529 (36%) | 124 (19%) | 85 (33%) | 84 (39%) | 236 (76%) |
| Persons with ≥1 fracture, n (% of total) | 212,449 (27%) | 367 (25%) | 185 (28%) | 68 (27%) | 43 (20%) | 71 (23%) |
| Persons with ≥2 fractures, n (% of total) | 80,470 (10%) | 141–151 (10%) | 74 (11%) | 38 (13%) | 0–10 (0–5%) | 29 (9%) |
| Persons with ≥3 fractures, n (% of total) | 38,776 (5%) | 76–86 (5–6%) | 35 (5%) | 29 (11%) | 0–10 (0–5%) | 12 (4%) |

Notes: ‡GMFCS II and III combined due to low numbers of fractures in some groups. §Interval to avoid data protection violation due to low number of fractures. †Gross Motor Function Classification System. ‡Epilepsy diagnosis (ICD-10 codes G40.0–G40.9) during follow-up.
Figure 1 Kaplan–Meier graph showing fracture-free survival of the background population (controls), ambulant children with CP (GMFCS I–III) and non-ambulant children with CP (GMFCS IV–V).

Figure 2 Age-specific fracture rates of Danish children with and without CP born 1997–2007.

Abbreviations: Ambulant CP, children with CP functioning at GMFCS levels I–III; Non-ambulant CP, children with CP functioning at GMFCS levels IV–V.
significant difference between children with CP and the background cohort was the high proportion of surgically treated fractures in GMFCS level V (z-test, \( p < 0.05 \)). A trend of fewer upper limb and more lower limb fractures was observed with increasing GMFCS level. In the background cohort 21% of fractures occurred in the lower limb and 74% in the upper limb. Compared to the background cohort, children with CP had significantly lower proportion of upper limb fractures in GMFCS groups IV and V (z-test, \( p = 0.0002 \) and \( p < 0.0001 \), respectively). The proportion of lower limb fractures was significantly higher in children functioning at GMFCS level V (z-test, \( p < 0.0001 \)). The proportion of fractures in the category of “Other fractures” was significantly higher in children functioning at GMFCS levels IV and V. This category included a variety of fracture codes including axial and unspecific fractures. However, it is noteworthy that vertebral fractures were rarely diagnosed in the CP cohort with less than 5 in each of the GMFCS groups. See Figure 3.

Turning to children with CP and comorbid epilepsy, we observed that fracture rates were increased (33.9 for boys, 32.8 for girls) compared to the total cohort of children with CP (26.7 for boys, 23.2 for girls). However, the fracture rates of children with epilepsy in the background cohort were higher (39.4 for boys and 33.7 for girls) than in children with CP and epilepsy. We observed the maximum fracture rates in both cohorts in children on long-term ASM treatment. Note that though the group with epilepsy and the group on long-term ASM treatment were likely overlapping, they were defined separately as described in Methods.

Children with CP on long-term ASM treatment had fracture rates of 38.9 for boys and 36.4 for girls, while the corresponding rates in the background cohort were 46.1 for boys and 45.2 for girls. When we stratified the results by ambulation, we found fewer fractures in the non-ambulant group. See Figure 4 for graphical comparison and confidence intervals. The number of fractures was inadequate for stratification by type of ASM.

Sensitivity analyses were performed to explore the number of fractures identified using grace periods of 90 and 150 days. The age-specific fracture rates were 0–6% higher using a 90-day grace period, while they were 0–4% lower using

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**Figure 3** Anatomical distribution of fractures in children with and without CP at GMFCS levels I–V. GMFCS levels II and III were combined due to low numbers. *Different from background cohort (z-test \( p < 0.001 \)).
During the initial 150-day grace period. When inspected graphically, the trends and the relationships between fracture rates of the groups (background, GMFCS I–III, GMFCS IV–V) were unchanged (see Supplementary Figure 1).

Discussion

In this study, we document that the fracture rates in children with CP are similar to peers in most age groups. The fracture-free survival of children with CP is comparable to the background population. To our knowledge, no previous study has directly compared whole-population fracture rates of children with CP to children without CP. As current literature and guidelines\(^1\) are based on higher fracture rates, our data provide a more accurate base to discuss pathways of fracture prevention.

In a prospective study, Stevenson et al\(^3\) followed 297 children with CP, GMFCS levels III–V, for 1.6 years (median) and reported yearly fracture rates of 4.0% based on 24 fractures. The yearly fracture rates were higher for children with a previous fracture (7.0%); for children with gastrostomy (6.8%) and for children with high triceps skinfolds (9.7%).

While this may be true for selected cohorts, lower fracture rates were demonstrated in the 2016 population-based study by Wort et al\(^5\), in which the yearly fracture rates of 152 children with severe CP (GMFCS IV–V) were calculated from 33 fractures over 9 years of register-based follow-up. The yearly fracture rates were 0.8% at age 0–4 years, 2.5% at age 5–9 years, 4.0% at age 10–14 and 3.0% at age 15–20 years. The fracture rates were compared to the general population using Standard Incidence Ratio (SIR) and the findings of a previous study from 1992 to 1993\(^22\) of the same geographical region. The SIR was reported to be 12.5% higher in children with CP; however, this difference was not statistically significant.

Our data stem from direct comparisons between Danish children with CP and the age-matched background population using the same registry criteria to define fracture in both cohorts. This approach results in a less biased comparison between the cohorts than in the previous studies. Our study includes the complete Danish population of...
children with CP and the entire, age-matched background population resulting in a higher number of participants and fractures than any previous study. Our results were unchanged in the sensitivity analyses. Importantly, our study documents that the pattern of fractures differs between the background population and children with CP regarding the location of the fractures. The increasing percentage of lower extremity fractures with increasing GMFCS level is probably related to the previously reported decrease in BMD with increasing GMFCS level. In fact, Wort et al demonstrated that the relative number of fractures occurring without trauma increases with higher GMFCS level. Thus, many fractures in non-ambulant children with CP are likely to be fragility fractures and possibly preventable by improvements to the bone health such as sufficient intake of calcium and vitamin D, physical activity or training as well as pharmacological interventions where needed.

Regarding gender differences, we find that males with CP had higher fracture rates than females, even in the category of non-ambulant children. The same pattern was seen by Henderson et al but not by Wort et al. This deserves consideration because the level of high-energy physical activity is very limited in both genders. The fact that non-ambulant males seem more prone to fractures suggests that physical activity may contribute only little to the fracture-rate difference between males and females in adolescence. In this way, our findings corroborate the hypothesis that pubertal hormones provide an important stimulus to the bones of non-ambulant children which supports monitoring and consideration of pubertal induction in cases of delayed puberty in young people with CP. The higher fracture rates of children with epilepsy and/or treated with ASMs may be attributed to the medication, to a high seizure burden or to other factors associated with epilepsy or ASM treatment. The same pattern was seen in ambulant and non-ambulant children with CP. The register data did not reveal whether fractures occurred in direct relation to seizures and the limited number of fractures in the CP cohort did not allow for comparison of fracture rates between specific drugs in CP patients. Taken together, our data support considering evaluating and optimizing bone health in all children with epilepsy, especially when treating with ASM.

Interestingly, we found that the most severely affected children with CP (GMFCS V) experienced a significantly higher incidence of fracture surgery than the background cohort. This finding suggests that the burden of surgical interventions may be higher in children with severe CP, and we find no evidence supporting the hypothesis of lower fracture surgery rates in children with CP.

This study has important limitations. We cannot exclude the possibility that fracture diagnoses were missed more often in children with severe CP than in children with less severe CP as fractures are likely to occur without trauma and many children with severe CP are non-verbal. We argue that while a diagnostic delay in children with severe CP may be common, fractures are unlikely to be missed entirely. Thus, we find that misclassification bias cannot be excluded but probably is a minor concern.

Regarding data quality and completeness in the National Patient Registry, validation studies have found a positive predictive value of 89% concerning orthopedic diagnoses and 82% on pediatric diagnoses. Additionally, we searched for fracture diagnoses in primary contacts as well as subsequent out-patient contacts, thus increasing the fracture detection rate. A diagnosis of epilepsy has a positive predictive value of 81.4 (95% CI 75.2–86.3) according to a 2007 validation study. A diagnosis of epilepsy may have been missed if the child was followed entirely in the primary care sector. If no long-term ASM was used then such a case would have been missed in both the epilepsy and the ASM groups. While this misclassification would probably be skewed towards mild cases of CP, we believe that very few children with any degree of CP and comorbid epilepsy are followed entirely in the primary sector in Denmark. Thus, the impact on our findings is likely trivial.

The databases used in this study have evolved over time, but no relevant changes were implemented in the period studied. The same diagnostic criteria and scoring methods were employed in Denmark during the study period regarding epilepsy, fractures, cerebral palsy and motor function.

A national follow-up program (CPOP) was implemented in 2010–2016 but included only children born after 2007. No new national guidelines concerning bone-health were issued during the study period. However, increased knowledge of the importance of vitamin D and calcium among physicians may have had preventive effect on fractures in children with CP.
The findings in this study reflect the Danish population and may be generalizable only to comparable populations in terms of CP incidence and etiologies, fracture epidemiology and healthcare system.

**Conclusion**

We find that children with CP despite their decreased physical activity have fracture rates similar to the background population. Fracture rates are not increased in non-ambulant compared to ambulant children with or without CP. However, a high proportion of lower extremity fractures with increased surgery rates suggests bone fragility and high fracture-related morbidity in non-ambulant children with CP. Epilepsy and long-term ASM treatment are associated with higher fracture rates in children with and without CP. This is useful information to caregivers and healthcare providers when weighing the risks versus benefits of therapies. Our data further support that pubertal changes reduce fracture rates in children with CP regardless of gender and motor function. Taken together, these findings indicate that fractures due to bone fragility in ambulant children with CP are similar to, and no more frequent, than fractures in the general population. Importantly, fractures in non-ambulant children with CP may be preventable by bone health screening and improvement strategies. Strategies may include monitoring and optimizing pubertal development and considering ASM treatments with minimal bone impact.

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