Skeletal maturation in children with cerebral palsy and its relationship with motor functioning

M van Eck, AJ Dallmeijer, JM Voorman, JG Becher
**ABSTRACT**

The objective of this study was to describe skeletal maturation in relation to chronological age in children with cerebral palsy (CP) aged 9 to 16 years, and to analyze the relationship between skeletal maturation and motor functioning. The skeletal age of 100 children with CP (37 females, 63 males; age 9, 11, or 13y; 73 ambulant, 27 nonambulant) was determined over a period of 3 years based on X-rays of the hand (Greulich and Pyle technique). Motor functioning was measured with the Gross Motor Function Measure-66. The skeletal age of females with CP was significantly higher than their chronological age, but this did not apply to males. Longitudinal analysis showed no difference in the course of skeletal age in relation to chronological age over a 3-year period for sex or for level of ambulation. No association was found between changes in skeletal age and changes in gross motor function over the 3-year period. Skeletal age during (pre-)puberty in females with CP is advanced in relation to chronological age. No evidence was found that children with CP are at risk for deterioration in gross motor function as a result of skeletal maturation during puberty.

**INTRODUCTION**

Little is known about the course of motor functioning in children with cerebral palsy (CP) during puberty and adolescence. The growth spurt and increase in body weight that take place during puberty in these children is suggested to lead to a deterioration in motor functioning. However, to our knowledge, the course of growth and possible deterioration in motor functioning during puberty and adolescence in this population have not yet been investigated.

Direct measurement of height to quantify a growth spurt in children with CP is often difficult or even impossible, due to contractures, skeletal deformities, or inability of the child to stand erect. Kong et al. found a strong association between skeletal age and linear skeletal growth in children with CP, and recommended that skeletal age with reference to the child's own chronological age should be used to describe growth. A reliable and simple method that can be used to measure skeletal age in growing children is the Greulich and Pyle technique. For this technique, an X-ray of the left hand is made and compared with a reference radiograph of a hand of a child of the same sex in the Greulich and Pyle atlas, and the skeletal age of the nearest match is assigned to the X-ray.

Skeletal growth abnormalities in children with CP have been found in several studies. However, the data are conflicting; some reported a delayed skeletal age in children with CP, while others reported a normal or even an advanced skeletal age. The majority of these studies have focused on children with severe CP, most of whom were non-ambulant. In these studies, no significant difference was found between skeletal and chronological age.
or a delayed skeletal age was found. Another study that focused on ambulatory children with CP reported an advanced skeletal age. Data on differences between males and females with regard to skeletal age in relation to chronological age are also conflicting. One study found no difference in skeletal age between females and males, while another study found a more advanced skeletal age in males than in females.

The aim of this study was to describe skeletal maturation in relation to chronological age in children with CP, aged 9 to 16 years, and to analyze the relationship longitudinally between skeletal maturation and motor functioning.

**METHODS**

**Participants**

The participants of this 3-year longitudinal study were recruited from rehabilitation centres, special schools for children with cognitive and physical disabilities, and outpatient clinics of departments of rehabilitation medicine in the North-west region of the Netherlands. Exclusion criteria were: insufficient knowledge of the Dutch language and the presence of additional disorders that have an important and lasting influence on movement skills. The study protocol was approved by all the regional Medical Ethics Committees and written informed consent was obtained from the participating children and their parents. This research was performed as part of the Pediatric Rehabilitation Research in the Netherlands programme (http://www.perrin.nl), which is a longitudinal study of functioning in children with CP.

**Data collection and measurements**

Skeletal age was determined mostly by a paediatric radiologist (78% of the X-rays) on the basis of an X-ray of the left hand using the Greulich and Pyle technique and the measurements were performed each year over a period of 3 years (four measurements). To assess the intrarater reproducibility of the Greulich and Pyle technique, X-rays of 26 children were scored a second time, by the paediatric radiologist, at least 1 year after the first measurement, using the same technique. In addition, a second assessment to determine skeletal age was performed by the same radiologist using the Tanner and Whitehouse method.

Motor functioning was assessed with the Gross Motor Function Measure (GMFM), which is a standardized observational instrument designed and validated to measure change in gross
motor function over time in children with CP. The GMFM score was analyzed with the Gross Motor Ability Estimator computer scoring program (GMAE) to obtain the GMFM-66 score. The GMAE rescales the child’s abilities from an ordinal scale to an interval scale, ranging from 0 to 100.

Severity of CP was classified according to the Gross Motor Function Classification System (GMFCS). The GMFCS is a 5-level classification system in which distinctions between the levels of motor functioning are based on functional limitations, the need for assistive devices and, to a lesser extent, quality of movement. Participants in our study were subdivided into two categories: ambulant children (GMFCS Levels I–III) and non-ambulant children (GMFCS Levels IV and V).

**Statistical analysis**

Descriptive statistics were used to describe skeletal age in relation to chronological age for each measurement. To determine differences in the course of skeletal age over a period of 3 years between males and females and ambulant and non-ambulant children, generalized estimated equations (GEE) were performed using the STATA statistical program (version 7.0). The GEE method considers the dependency of repeated measures within one person and allows for a variable number of observations per person. For these analyses, skeletal age minus chronological age was the dependent variable and sex, level of ambulation, and the interaction terms of those variables with time were the independent variables. Level of ambulation and age group were included as possible confounders in the model with sex, and sex and age group were included as possible confounders in the model with level of ambulation.

An autoregressive GEE model was used to analyze the influence of changes in skeletal age on changes in gross motor function. In an autoregressive model, outcome at each measurement is adjusted for the outcome at the previous measurement (i.e. GMFM-66 at measurement time (T) is adjusted for GMFM-66 at T1). For these analyses, GMFM-66 was the dependent variable, and skeletal age minus skeletal age at the previous measurement (Δ skeletal age) and GMFM-66 at the previous measurement were the independent variables. If necessary, the analyses were adjusted for sex, level of ambulation, age group, and the interaction term of those last three variables with Δ skeletal age. For all analyses, a statistical significance of $p < 0.05$ was assumed.
RESULTS

The rehabilitation centres, special schools for children with cognitive and physical disabilities, and outpatient clinics of departments of rehabilitation medicine identified 244 children aged 9, 11, and 13 years with CP. Of the 110 children whose parents consented to participate, 100 children (37 females, 63 males, 73 ambulant, 27 non-ambulant) had two or more hand X-rays over a period of 3 years and were included in the analyses. Children were all of Dutch Caucasian origin.

The characteristics of the participants are presented in Table 2.1. Of the 100 children who were included in the analyses, 83 participated in all four measurements, 15 children participated in three measurements, and two children participated in two measurements. Children with missing observations did not differ in characteristics from the total group.

<table>
<thead>
<tr>
<th>Table 2.1 Baseline characteristics of the 100 children with cerebral palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Age group, y</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>Level of ambulation</td>
</tr>
<tr>
<td>Ambulant\textsuperscript{a}</td>
</tr>
<tr>
<td>Non-ambulant\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Children in Gross Motor Function Classification System (GMFCS) Levels I to III; \textsuperscript{b} children in GMFCS Level IV and V.

Skeletal age

The intraclass correlation coefficient (ICC) for the repeated measurements \((n = 26)\) with the Greulich and Pyle technique was high: 0.96 (95% confidence interval [CI] 0.92–0.98). Comparison of this technique with the Tanner and Whitehouse technique also showed a high ICC of 0.90 (95% CI 0.79–0.96).

We found a high prevalence of participants with a more than 1-year delayed or advanced skeletal age in relation to chronological age (Table 2.2). Of the males, 42 to 55% had a skeletal age deviating 1 year or more from their chronological age, and for the females this percentage was 38 to 57%. Only a small percentage of females had a delayed skeletal age, whereas the percentages of delayed and advanced skeletal age in males were more equally divided.
The course of skeletal age and chronological age for females is shown in Figure 2.1, and for males in Figure 2.2. GEE analyses showed a significant difference in skeletal age in relation to chronological age (skeletal age minus chronological age) between males and females, with an overall higher skeletal age minus chronological age of 0.69 years in females. However, no difference between males and females was found in the course of skeletal age in relation to chronological age over a 3-year period. The results were the same when adjusted for level of ambulation and age group. No significant difference was found in the course of skeletal age in relation to chronological age between ambulant and nonambulant children. The results were the same when adjusted for sex and age group.

## Changes in gross motor function

Overall, gross motor function remained stable over the 3 years, although some children deteriorated while others improved. GEE analyses showed no association between changes in skeletal age and changes in gross motor function. We expected to find a negative regression coefficient, indicating that a larger increment in skeletal age was associated with a smaller change in GMFM. However, the regression coefficient of –0.36 was not statistically significant ($p = 0.180$). Sex and level of ambulation and their interaction with Δ skeletal age had no effect on these results.

### Table 2.2 Percentages over 1 year of advanced and delayed skeletal age in relation to chronological age in children with cerebral palsy

<table>
<thead>
<tr>
<th>Time (T) of measurement</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1y advanced skeletal age, $n$ (%)</td>
<td>&gt;1y delayed skeletal age, $n$ (%)</td>
</tr>
<tr>
<td>T0</td>
<td>8/62 (13)</td>
<td>18/62 (29)</td>
</tr>
<tr>
<td>T1</td>
<td>13/62 (21)</td>
<td>15/62 (24)</td>
</tr>
<tr>
<td>T2</td>
<td>14/60 (23)</td>
<td>19/60 (32)</td>
</tr>
<tr>
<td>T3</td>
<td>14/55 (26)</td>
<td>12/55 (22)</td>
</tr>
</tbody>
</table>

* Children in Gross Motor Function Classification System (GMFCS) Levels I to III; †children in GMFCS Level IV and V.
Figure 2.1  Means of skeletal and chronological age at four measurements for females. Females had a significantly higher skeletal age than their chronological age at all measurements.

Figure 2.2  Means of skeletal and chronological age at the four measurements for males. There was no significant difference between skeletal age and chronological age at any of the measurements.
DISCUSSION

The first aim of this study was to describe skeletal maturation in relation to chronological age in children with CP aged 9 to 16 years, over a 3-year period. There was a high prevalence of children whose skeletal age was advanced or delayed in relation to their chronological age. The percentages found in our study differed from those reported by Kong et al. who found that 68% of the children with CP had a delay of more than 1 year in skeletal age compared with only 11 to 32% in our study. In contrast, Gollapudi et al. found that 94% of the ambulatory children with CP in their study had an advanced skeletal age compared with their chronological age, and 35% had an advanced skeletal age of more than 3 years. These conflicting findings may be explained by sex, because in our study we found that skeletal age in females with CP was significantly higher than their chronological age at all four measurements, but this did not apply to males. Worley et al. found that children with CP enter puberty earlier, but end puberty later, compared with healthy controls. This might suggest hormonal alterations, which might also contribute to the advanced skeletal maturation found in females in our study. It has been found that some children with CP have abnormalities in growth hormone secretion. It is also known that females with other neurological disorders, such as myelomeningocele and spina bifida, often enter puberty at an early age, probably as a result of hormonal disturbances. In previous studies, sex was also found to be an important factor for skeletal age.

In addition to sex, the conflicting findings about delayed or advanced skeletal age in children with CP might be explained by the age range of the study population, which was small in our study, whereas Kong et al. and Gollapudi et al. studied an age range of approximately 2 to 16 years. Another factor which may also explain the conflicting findings, is the severity of CP. Studies on non-ambulant as well as ambulant children with CP are conflicting regarding advanced or delayed skeletal age in children. We did not find any difference in skeletal age between the (non-ambulant) children with more severe CP and the (ambulant) children with less severe CP. Finally, the method used to determine skeletal age may also have affected the results. Kong et al. used the Tanner and Whitehouse method and Gollapudi et al. used the Oxford method, in which an X-ray of the pelvis is assessed instead of an X-ray of the hand.

The higher skeletal age compared with chronological age found in females in our population deviates from the difference in skeletal age and chronological age in the typically developing Dutch Caucasian population. The study of van Rijn et al. found an average retardation in skeletal age compared with chronological age of 1.7 months in healthy Dutch females and 3.3 months in healthy Dutch males, while we found, on average, an advanced skeletal age of 6.3 months in Dutch Caucasian females with CP.
The course of skeletal age in relation to chronological age over a 3-year period did not differ with sex, even after correction for age and level of ambulation. Neither did it differ for level of ambulation, also after correction for age and sex. To our knowledge, the course of skeletal maturation in relation to chronological age in either more or less severely impaired children with CP has not been investigated before in a prospective longitudinal study. Previous studies have reported either retrospective or cross-sectional results.4,8,10,11

The second aim of this study was to analyze the relationship between skeletal maturation and motor functioning. No evidence was found that children with CP are at risk for deterioration in gross motor function as a result of skeletal maturation during puberty. The possible deterioration in gross motor function during puberty could be influenced by factors other than skeletal maturation. Factors representing development in puberty, such as increase in height, changes in body mass index, Tanner stage, and hormone levels might influence gross motor function. Increase in height was not taken into account in the present study because this is difficult to measure in more severely impaired children with CP. However, alternative factors, such as knee height, upper arm length, and CP-specific growth curves could be used.21 Multiple, interacting factors could also contribute to a decrease in motor functioning, such as specific impairment characteristics (e.g. lack of selective motor control), and personal and environmental factors. Voorman et al.22 found that the children with more severe CP had a less favorable course in motor functioning. Further longitudinal research should be carried out to investigate possible associated factors that influence motor functioning during puberty.

As a limitation of this study, it should be mentioned that the cohorts of children with CP were 9, 11, and 13 years old, which means that some children had already entered puberty while others had not. It is possible that children in the 11- and 13-year cohorts had already undergone their growth spurt. Furthermore, it is known that some females with CP enter puberty before the age of 9,18 but we did not assess the onset of menarche or Tanner stage in our study. It is possible that some of the females with CP had entered puberty and had their growth spurt before the age of 9, thus, before they were included in our study. Therefore, in future longitudinal studies of children with CP during puberty we recommend the inclusion of children younger than 9 years of age.

**Conclusion**

A large percentage of children with CP had a skeletal age that deviated by 1 year or more from their chronological age. Skeletal age during (pre-)puberty in females with CP was
advanced in relation to chronological age. No difference was found in the course of skeletal age in relation to chronological age over a 3-year period for sex or level of ambulation. Furthermore, we found no evidence that children with CP are at risk of deterioration in gross motor function as a result of skeletal maturation during puberty.

**Acknowledgements**

This research was performed as part of the Pediatric Rehabilitation Research in the Netherlands (PERRIN) research programme. The project was supported by the Netherlands Organization for Health Research and Development (grant number 1435.0028). We are also very grateful to Jonathan IML Verbeke, radiologist, for his support in scoring the X-rays.
REFERENCES


