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Scoliosis in children with osteogenesis imperfecta: influence of severity of disease and age of reaching motor milestones

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Abstract We studied the relationship between the age of reaching motor milestones, especially anti-gravity activities, and the age of development of pathological spinal curvatures in children with osteogenesis imperfecta (OI). We hypothesized that earlier achievement of anti-gravity motor milestones predicts a later development of pathological spinal curvatures. Ninety-six children participated in this retrospective study. The severity of the disease was classified according to Sillence into types I–IV. Spinal radiography was performed annually and spinal deformities were measured according to the Cobb angle. Scoliosis was defined as a Cobb angle exceeding 9°. Pathological thoracic kyphosis was defined as a Cobb angle exceeding 40°. The parents were asked to report the age at which the child achieved motor milestones, and data were checked against health care records. Thirty-seven of 96 children (39%) developed a scoliosis of more than 9°. Nine of 96 children (9%) developed a pathological kyphosis. The age of developing scoliosis was significantly lower than the age of development of the pathological kyphosis ($P=0.01$). Bone mineral density was measured by dual energy X-ray absorptiometry (DEXA) in 53 children, 28 of whom developed scoliosis, and 25 of whom did not. The mean DEXA Z-score of the 28 children with scoliosis was significantly lower than that of the 25 children without (-5.2 , SD 1.3 vs -3.2 , SD 1.9; P -value <0.001). Children with OI type IV, but particularly OI

type III, reached motor milestones much later than children with OI type I. The motor milestone “supported sitting” showed a significant inverse association with time of the first presence of scoliosis with a Cobb angle greater than 9° (linear regression coefficient: -1.3 , 95% confidence interval: -2.6 to -0.03). The age of achieving the motor milestones “lifting the head to 45° in prone position”, “rolling”, and “supported-” and “unsupported standing” were not significantly associated with age of the first presence of scoliosis with a Cobb angle greater than 9°. However, the directions of associations suggest that here, too, there is a tendency for later development of scoliosis in those who reach milestones at earlier ages. Multivariable analyses showed that the motor milestone “sitting with support” was significantly associated with age of first achieving scoliosis, independent of gender and type of OI (linear regression coefficient: -0.9 , 95% confidence interval: -1.3 to -0.5). We conclude that in children with OI, the age of anti-gravity motor milestones was associated with the age of development of pathological spinal curvatures. Earlier achievement of the motor milestone “supported sitting” predicted significantly a later development of pathological spinal curvatures, independent of gender and type of OI.

Keywords Osteogenesis imperfecta · Scoliosis · Motor development · Anti-gravity motor milestones

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Introduction

Osteogenesis imperfecta (OI) is a congenital connective tissue disorder, which probably affects 1 in 5,000 to 10,000 individuals without racial or ethnic preference [3]. Major clinical characteristics of OI include fragility of bone, osteopenia, variable degrees of short stature, and progressive skeletal deformities. Additional clinical manifestations are blue sclerae, dentinogenesis imperfecta, joint laxity, and maturity-onset deafness [22]. OI is subdivided into four types (I, II, III, IV), based on clinical, radiographic and genetic characteristics according to Sil- lence [20, 21].

The prevalence of spinal deformity in OI depends on the system of classification used, and has been reported at between 15 and 92% [2, 5, 8, 10, 11, 14].

Patients with the severest types of OI have a higher incidence of scoliosis. Benson and Newman state that scoliosis is rare before the age of 6 years. After this age, a rapid progression of scoliotic deformity is observed [1].

The etiology of spinal curvatures in children with OI remains disputable. Benson and Newman stated that the laxity of spinal ligaments plays a role in lack of vertebral stability and allows for progressive spinal curvature [1]. Ishikawa et al. found that the vertebral body shape is a predictor of spinal deformity in OI [11].

Scoliosis usually progresses until severe kyphoscoliosis is present in adulthood [15, 16]. Severe scoliosis and concomitant chest deformity will interfere with self-care, mobility and pulmonary functions, and may be an indication for spondylodesis [12, 23].

The proprioceptive system that influences posture seems to play an important role in spinal balance during growth [13]. The development of the proprioceptive system starts as soon as we can move, and continues until adulthood. The development of this system in childhood is an integral part of motor development. Although the age of reaching motor milestones in the different OI types has been described in detail, and prognostic influences of the age of reaching motor milestones on level of ambulation have been studied, interactions between the age of reaching motor milestones and the incidence of spinal curvatures at later age has never been studied [6, 7].

The purpose of this study was to investigate the relationship between the age of reaching motor milestones, especially anti-gravity activities, and the age of development of pathological spinal curvatures. We hypothesized that earlier achievement of anti-gravity motor milestones predicts a later development of pathological spinal curvatures.

Materials and methods

Ninety-six children who attended the outpatient clinic for children with OI at the Wilhelmina Children's Hospital participated in this

retrospective study. Our hospital is a national center for diagnosis, treatment and research for children with OI.

Children were included if the diagnosis was clear and the severity of the disease could be classified according to Sil- lence [20, 21] (type I: $n=57$, boys/girls: 26/31; type III: $n=18$, boys/girls: 10/8; type IV: $n=21$, boys/girls: 9/12). Their mean age was 11.1 years (SD 4.8 years). Children younger than 2 years of age were excluded because not all developmental milestones might have been reached. Children who used bisphosphonates were also excluded from this study, since this medication may interfere with bone mineral density and thereby possibly influence the age of first appearance of scoliosis.

In children with type I, III or IV OI, spinal radiography was performed annually. If scoliosis was present, radiographic follow-up was performed once a year, or more frequently when indicated. The spinal deformities were measured according to the Cobb method on postero-anterior radiographs. If two curves were present, the greater curve was used for analysis of data.

Scoliosis was defined as a Cobb angle exceeding 9° [19].

Thoracic kyphosis was measured according to Cobb and compared to reference values for children. A kyphosis of more than 40° was considered pathological [17].

Bone mineral density (BMD) was measured in a standard way using the dual energy X-ray absorptiometry (DEXA) method and expressed as Z-scores (normal between -2 and 2).

A postal questionnaire was sent to the parents with questions regarding the age at which patients reached the following motor milestones:

- Lifting the head to 45° in prone position
- Rolling from prone to supine
- Supported sitting
- Unsupported sitting
- Coming to a sitting position independently
- Supported standing
- Unsupported standing

We urged the parents to be as precise as possible in the retrieval of their child's age of reaching the motor milestones and advised them to check this with available data from primary health care centers. If parents were not sure, we advised them not to fill in the age of a certain motor milestone, but to report their doubt concerning the age. If motor milestones were not achieved at all, this also had to be reported.

Almost all children of this study visited our hospital from birth or early childhood on (OI type I: once a year; OI types III and IV: two times a year or more frequently when indicated). During these visits, clinical examinations were performed and data concerning motor development were gathered. All data, obtained from the postal questionnaire were checked against healthcare records by the first author. If parents did not know the age of achieving a certain motor milestone, and the age of this milestone was recorded in healthcare records, the latter was used for analysis. If comparison of the age of reaching certain milestones of the parental questionnaire with healthcare records revealed a discrepancy of more than 3 months, this item was excluded from the study.

Statistical analysis regarding differences in age of spinal curvature occurrence between the different types of OI was carried out using the Mann-Whitney U test. Differences in age of reaching motor milestones in children with type I OI between those who did and those who did not develop a pathological scoliosis were also analyzed using the Mann-Whitney U test. The association between the age of developing a scoliosis and the age of achieving motor milestones was analyzed using linear regression. The age when the scoliosis was first detected was used as the dependent variable. The age of achieving developmental milestones, type of OI, gender and age were studied as predictors. First, univariable analysis was performed (Table 3), followed by multivariable analysis (Table 4). The regression coefficients were considered significant when their 95% confidence intervals did not include zero, indicating that the

Table 1 Characteristics of the 96 patients with osteogenesis imperfecta (OI) who were included in the study. DEXA (dual energy X-ray absorptiometry) scores were available in 53 children

	OI type I (n=57)	OI type III (n=18)	OI type IV (n=21)
Scoliosis >9° according to Cobb	11 (19%)	13 (72%)	13 (61%)
Mean age (SD)	7.0 (5.0)	6.8 (3.4)	9.0 (3.9)
Boys/girls	5/6	8/5	7/6
Kyphosis >40°	3 (5%)	2 (11%)	4 (19%)
Mean age (SD)	10.9 (5.3)	8.8 (3.2)	13.6 (2.1)
Boys/girls	3/0	1/1	3/1
Mean Z-score (SD) DEXA, scoliosis: yes	-4.5 (1.2) (n = 6)	-6.3 (0.7) (n = 8)	-4.6 (1.3) (n = 11)
Mean Z-score (SD) DEXA, scoliosis: no	-3.1 (1.9) (n = 22)	-4.1 (2.5) (n = 3)	-3.2 (1.6) (n = 3)

coefficient is different from zero with an α error rate of less than 5%.

Results

Patient characteristics are presented in Table 1. Thirty-seven of 96 children (39%) developed a scoliosis. As expected, many more children with OI type III or IV developed scoliosis. The mean age of the first radiographic diagnosis of a scoliosis was somewhat higher in OI type IV patients. Nine of 96 children (9%) developed a pathological kyphosis. The age of developing scoliosis was significantly lower than the age of developing a pathological kyphosis ($P=0.01$).

DEXA measurements were available in 53 children, 28 of whom developed scoliosis, and 25 of whom did not. The mean DEXA Z-score (SD) of the 28 children with a scoliosis was significantly lower than that of the 25 children without (-5.2 , SD 1.3 vs -3.2 , SD 1.9; P -value <0.001).

Seventy-six (79%) of the 96 parents who were sent questionnaires responded. Data of the age of reaching anti-gravity motor milestones in children who developed a scoliosis of more than 9° are presented in Table 2. Children with OI type IV, but particularly OI type III, reach motor milestones much later than children with OI type I. In children with type III, supported and unsupported standing were not reached in the majority of the patients.

Comparison of children with OI type I in whom the age of developmental milestones was known with the

children in whom the age of developmental milestones was not known revealed no significant differences with respect to the age of development of scoliosis.

At the moment of retrospective analysis, mean age of the children with type I who did not develop a pathological scoliosis was 8.6 years (SD 4.5 years), while the mean age of the children with type I who developed a pathological scoliosis was 11.0 years (SD 5.1 years; P -value: 0.07). No significant differences between the age of reaching motor milestones in children who did and those who did not develop a pathological scoliosis were present. Comparison of children with OI type III and IV in whom the age of developmental milestones was known with the children in whom the age of developmental milestones was not known or not present revealed no significant differences with respect to the age of development of scoliosis.

Since almost all children with OI type III or IV developed a pathological scoliosis, no meaningful comparison of those who developed with those who did not develop a scoliosis could be performed.

Table 3 shows general characteristics and motor milestones as predictors of the age at first occurrence of scoliosis. The motor milestone "supported sitting" showed a significant inverse association with time of the first presence of scoliosis (linear regression coefficient: -1.3 , 95% CI: -2.6 to -0.03 ; $P=0.04$). The motor milestones "lifting the head to 45° in prone position", "rolling", and "supported" and "unsupported standing" were not significantly associated with age of the first presence of scoliosis. How-

Table 2 Age of achieving motor milestones in children with scoliosis related to the different types of OI ($P50$ 50th percentile, $P25$ – $P75$ 25th to 75th percentile)

Motor milestones	OI type I (N=11)			OI type III (N=13)			OI type IV (N=13)		
	n	Age (months)		n	Age (months)		n	Age (months)	
		P50	P25–P75		P50	P25–P75		P50	P25–P75
Lifting head to 45° in prone position	10	4	3–6	5	40	14–96	7	3	3–8
Rolling	7	6.5	5–9	6	42	33–75	8	9	8–12
Supported sitting	9	7	5–9	7	40	15–55	9	11	8–20
Unsupported sitting	10	9	8–10	6	31	24–58	11	12	10–15
Supported standing	9	12	11–15	3	51 ^a	49–84 ^a	11	16	12–26
Unsupported standing	11	16	12–18	2	106 ^a		11	18	15–30

^a The age of (un)supported standing in OI type III has to be interpreted with caution because of the limited number of children who are able to reach these milestones

Table 3 Results of univariate analysis in children with OI between predictors and age of first achieving scoliosis: linear regression coefficients and 95% confidence intervals (CI). Statistically significant associations were considered reached when the 95% CI did not include the null value, and are shown in *bold*

	Linear regression coefficient	95% CI
Gender	3.4	−30.4, 37.2
Type of OI	7.1	−6.5, 20.7
Motor milestones		
Lifting head to 45° in prone position	−0.3	−1.1, 0.5
Rolling from prone to supine	−0.06	−0.8, 0.7
Supported sitting	−1.3	−2.6, −0.03
Unsupported sitting	−0.6	−1.8, 0.6
Supported standing	−0.06	−1.1, 1.0
Unsupported standing	0.3	−0.5, 1.0

Table 4 Results of multivariable analysis in children with OI between predictors and age of first achieving scoliosis. Statistically significant associations were considered reached when the 95% CI did not include the null value and are shown in *bold*

	Linear regression coefficient	95% CI
Lifting the head to 45° in prone position	−0.2	−0.6, 0.2
Gender	9.8	−12.0, 32.4
Type	−9.4	−18.2, −0.6
Rolling from prone to supine	−0.1	−0.5, 0.2
Gender	5.1	−17.6, 27.9
Type	−7.5	−17.3, 2.1
Supported sitting	−0.9	−1.3, −0.5
Gender	3.0	−11.5, 17.7
Type	−5.1	−11.5, 1.3
Unsupported sitting	−0.4	−1.0, 0.15
Gender	6.0	−13.7, 25.9
Type	−7.5	−0.7, 0.4
Supported standing	−1.4	−0.7, 0.4
Gender	5.2	−15.5, 26.1
Type	−6.8	−15.0, 1.4
Unsupported standing	−0.08	−0.4, 0.2
Gender	7.8	−12.2, 27.8
Type	−8.5	−16.0, −1.2

ever, the directions of associations suggest that here, too, there is a tendency for later development of scoliosis in those who reach milestones at earlier ages. The type of OI and gender were not significantly associated with time of the first presence of pathological scoliosis.

Thus, the analysis showed that the motor milestone “sitting with support” was the most important univariate predictor of the age of development of scoliosis.

Subsequently, we assessed the extent to which the association between milestones and scoliosis were independent of general patient characteristics. The multivariable analyses in Table 4 show that the motor milestone “sitting with support” was significantly associated with age of first achieving scoliosis, independent from gender and OI type.

Discussion

Secondary scoliosis can be caused by any one in a long list of primary diseases. In congenital malformations and collagen diseases, the etiology of progressive scoliosis is clear. In OI it is logical that the collagen abnormality causes hypermobility of the spinal ligaments, as well as deformations of the vertebral bodies during lifetime. The high incidence of scoliosis in OI supports this theory. Nonetheless, in children with OI, especially with the severest forms, not every patient develops spinal deformity, although all show platyspondyly and hypermobility.

The results of the DEXA measurements showed significant differences between the children with and those without a scoliosis. This significant difference in BMD is primarily due to the type of OI, since 76% (19 of 25) of the children with type III or IV who developed a scoliosis had a severe decrease in BMD compared to the 21% (6 of 28) with type I who developed a scoliosis. This indicates that the role of BMD in the development of scoliosis is an important factor. The other factor is motor development, and this is proved by some children having no scoliosis and very low BMD.

In idiopathic scoliosis, a multifactorial cause seems to exist, in which maintaining spinal balance during growth is crucial [19]. The proprioceptive system that influences our posture seems to play an important role [13]. The training of the proprioceptive system starts as soon as we can move, and continues till adulthood [9]. The influence of a delayed or a poorer performing proprioceptive system is clearly demonstrated by the high incidence of idiopathic scoliosis in children with retarded motor development [18]. In this study, we demonstrate the influence of posture control by the analysis of motor development in children with OI and the prevalence of scoliosis.

It is evident that the most important factor is the collagen disease itself, as the incidence of scoliosis rises with the severity of the disease. But the results of this retrospective analysis show a significant association with developmental motor milestones in these children. Early spinal balance, in particular, as illustrated with the motor milestone “supported sitting”, is related to the age of first achieving spinal deformities.

The importance of age of reaching motor milestones has also been studied in relation to walking capacity. Reaching the motor milestone “independent sitting” by the age of 10 months is a predictor of walking as the main means of mobility in 76% of OI patients [4].

Another retrospective study regarding the age of reaching motor milestones on the ability to walk illustrated that the motor milestones “rolling over before 8 months”, “unsupported sitting before 9 months”, “ability to get in sitting position without support before 12 months” and “ability to get in a standing position without support before 12 months” showed significant associations with the ability to walk, especially when the type of OI is uncertain [7].

This study has intrinsic limitations. First of all, although data are gathered on a national basis, the sample size of our study is small and limits the power of the statistical analysis. This may be the reason why several motor milestones were not significantly associated with age of the first presence of scoliosis of greater than 9° Cobb angle. However, the directions of associations between motor milestones and scoliosis suggest that there is a tendency for later development of scoliosis in those who reach milestones at earlier ages.

Secondly, the use of parental reports may introduce a bias, since the postal questionnaires were filled out at a time quite distant from the actual events. This bias may have occurred in about 20% of our population, mainly in children with OI type I, who visited our hospital for diag-

nosis of frequent fracturing when they were already walking. The other children visited our hospital at least annually from birth or early childhood on, where data regarding motor development, based on physical examination, were gathered.

Although in OI the collagen synthesis is disturbed, it is probable that influencing the proprioceptive system by training the motor development would increase the age of development of scoliosis. Further studies to investigate this possibility would be valuable.

Conclusion

We conclude that in children with OI, the age of achieving motor milestones, especially anti-gravity activities, are associated with the age of development of pathological spinal curvatures. Earlier achievement of the motor milestone “supported sitting” predicted significantly a later development of pathological spinal curvatures, independent of gender and type of OI.

We also conclude that BMD is an important factor in the development of scoliosis.

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