Osteogenesis Imperfecta: A Clinical Study of the First Ten Years of Life

U. Vetter, B. Pontz, E. Zauner, R. E. Brenner, and J. Spranger

Summary. One hundred twenty-seven children with osteogenesis imperfecta (O.I.) were studied during the first 10 years of life. According to Sillence, 40 patients were assigned to type I, 39 to type III, and 48 to type IV O.I. Centiles for height, weight, and the annual number of fractures could be established for the different types of O.I. The development of the skeletal changes could be documented for the different forms of the disease. At birth, the skeletal changes were significantly more severe in type III than in type IV patients. During the first 10 years of life the number of fractures, extent of skeletal deformities, and growth retardation did not differ between types III and IV. Only fracture nonunion, dentinogenesis imperfecta, and congenital cardiac malformations were more frequent in type III than in type IV. Papillary calcifications of the kidney and kidney stones were diagnosed in 4 type III and 2 type IV patients. Hemihypertrophy of the body developed in 2 type I patients. Although types III and IV patients suffered from severe short stature, serum insulin-like growth factor (IGF) I was in the normal range.

Key words: O.I. childhood - Clinical course - Classification.

Osteogenesis imperfecta (O.I.) is a congenital disease of connective tissue, most likely the result of point mutations, insertions, or deletions in the genes coding for the α1 (I) and α2 (I) chains of type I collagen [1-3]. O.I. is characterized by bone fragility, osteopenia, variable degrees of short stature, and progressive skeletal deformities. Blue sclerae, dental abnormalities, joint laxity, and maturity onset deafness can be additional manifestations.

Sillence et al. [4] have identified four clinical/hereditary subgroups in this disease. Type I and Type IV patients show an autosomal dominant inheritance and mild or moderate skeletal abnormalities. Type I patients show distinctly blue sclerae, whereas the sclerae of type IV patients are white. Type II is the most severe form of O.I., resulting in intrauterine or perinatal death. Type III patients have severe skeletal abnormalities, but usually live to adulthood. The sclerae of type III patients are usually blue in early infancy and white in later life. Although types II and III were originally designated as autosomal recessive conditions, it is apparent that they are genetically heterogeneous [5, 6].

We have analyzed the clinical course of 127 patients diagnosed in the first 2 years of life and have assigned them to types I, III, and IV O.I. This report provides new data on growth, fracture rates, and the incidence of major skeletal and extraskeletal changes.

Patients and Methods

All patients were diagnosed in the first 2 years of life and were seen at 1-year intervals for clinical evaluation. They all were of Caucasian origin, mainly German, but 6 patients from Austria, Switzerland, and Italy, and 4 from Turkey were also included. The height was measured in the recumbent position. Fractures were documented primarily by radiographs. Motor performance was scored at each visit using the major motor milestones (sitting erect unsupported, wheel chair control, ambulation with and without crutches). Neonatal history and radiographs of all types III and IV patients were obtained from the local hospitals. Echocardiographic and sonographic examinations of the kidneys were performed with an ULTRAMARK 8 (ATL, Bothell, USA). Insulin-like growth factor I (IGF I) was measured by RIA (Immuno Nuclear, Hamburg, FRG).

Forty patients suffering from type I O.I. showed blue sclerae throughout infancy; 30 of them had a family history of O.I. The affected parents showed mild disease. Thirty-nine patients suffered from type III O.I. Blue sclerae present early in infancy turned white during the first 2 years of life. The family history of 4 patients revealed only siblings who also suffered from type III O.I. Forty-eight patients suffering from type IV O.I., sclerae were white from birth in both the 33 nonfamilial cases and in the 15 patients with a family history of O.I. The affected parents showed a variably severe O.I. No siblings with O.I. were found in these families. Eighteen additional patients could not be classified and are not reported.

Statistics

Data are presented as the median, the 5th, 25th, 75th, and 95th centiles. Statistical comparison of different groups of patients was performed by the Wilcoxon test.

Results

Manifestation at Birth and During Neonatal Period

Normal birth weights and lengths were found in type I and IV. The birth weights and lengths of type III patients were significantly lower than in types I and IV (z < 0.05). The head circumference was largest in type I (z < 0.05), but...
normal compared with age-matched controls. Caesarian sections were frequently performed in all O.I. types because of breech presentation (Table 1). The duration of pregnancy was normal in all types.

At birth, type III patients showed a significantly higher incidence of deformities of the upper and lower extremities than the other O.I. patients (z < 0.05; Table 1). Radiographs of the skull showed no Wormian bones in 30% of type I patients. The number of fractures and the skeletal changes at birth were significantly more frequent in type III than in type IV patients (z < 0.05; Table 2).

Development of the Skeletal Manifestation During the First Decade of Life

Only 15% of type I patients developed deformities of the long bones and 24% developed kyphoscoliosis (Cobb angle 25–40°). Two type I patients showed left-sided hemihypertrophy, defined as unilateral overgrowth of the body, including the structures of the head, trunk, and limbs [7]. Type III patients did not develop new deformities of the lower extremities, whereas new deformities of the upper extremities were observed in some type III patients. New deformities of both the lower and upper extremities developed in type IV patients during the first 10 years of life.

More type IV than type III patients suffered from kyphoscoliosis (z < 0.05; Table 4) (Cobb angle 40–70°). In 50% of the type III patients the radiographic appearance of ribs changed from a very thin shape in the perinatal period to a thickened shape early in life. Later the shape was thin again. Pseudoarthroses were most frequent in patients with type III (z < 0.05). Deformity of the pelvis developed more frequently in type III than in type IV patients (z < 0.05). Cystic changes of the epiphyses and metaphyses (also called "popcorn epiphyses") are the result of a disturbed endochondral bone formation causing incomplete replacement of the growth plate cartilage [8]. This and hyperplastic callus formation were observed in both type III and type IV patients (Table 3).

Occurrence of Fractures

Type I patients suffered from significantly few fractures than type III and IV patients (z < 0.05), who had approximately the same fracture rate (Fig. 1).

Body Growth

The median of height and weight followed the 3rd centile of normals in type I [9]. In types III and IV patients, the growth rate was greatly reduced from birth to about 6–7 years of age and stopped thereafter almost completely (Fig. 2A–C).

Motor Performance

Motor development was delayed in type I patients; however, at the age of 4 years, 70% of them ambulated independently. At that age, one-third of the type IV patients were able to walk on crutches, whereas only 50% of type III patients were able to sit without assistance. At the age of 10 years, almost 80% of type III patients were able to sit without assistance and 20% were able to walk short distances on crutches (Table 3).

Extraskeletal Manifestation

Dentinogenesis imperfecta was diagnosed in 50% of the types I and IV and more than 80% of the type III patients. Cardiac malformations (3 ASD II, 2 VSD, 1 aortic stenosis, 1 Fallot's tetralogy) were diagnosed by echocardiography in 7 patients. The highest incidence of cardiac abnormalities was found in type III patients (z < 0.05). In 6 patients, kidney stones and renal papillary calcifications were detected by ultrasonography (Table 4).

IGF I Serum Levels

Serum concentrations of IGF I in 63 patients were in the normal to low normal physiological range. The serum concentrations were in the hypopituitary range only in 2 patients (< 40 ng/ml) [21, 22] (Fig. 3).

Mortality

During the study, 5 type III patients with instability of the thorax died due to respiratory failure and staphylococcal pneumonia. One type IV patient died because of primary pulmonary hypertension.

Discussion

Few longitudinal studies of distinct O.I. subtypes have been performed [10–13]. The Silence classification [4] provides criteria for such a study, although we are aware that this clinical/hereditary classification has certain limitations in the light of the underlying genetic defects of O.I. Our longitudinal study reports for the first time centiles for height, weight, and annual number of fractures in a large number of different types of young O.I. patients.

As reported earlier [4, 5, 8, 10], type I patients did not