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Osteogenesis Imperfecta: Report of 2 Cases

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Osteogenesis imperfecta is a rare, inherited disorder of connective tissue. Although many organs are affected, the major feature of the disease is bone fragility. Patients severely affected may have hundreds of fractures, the majority of which occur prior to puberty. The apparently multiple heredity patterns associated with this disease may account for the wide variety of clinical features. The first case reported here shows a previously unreported association of fetal ascites obscuring an antenatal diagnosis of osteogenesis imperfecta type II by ultrasonography. The second case appears to be a milder expression of osteogenesis imperfecta type II, with no evidence of fractures until delivery. Debate continues over the genetic and prognostic heterogeneity of this disease. Management is limited to aggressive fracture care with the emphasis on early weight-bearing to prevent immobilization osteoporosis and maximizing long-term mobility. The problems in genetic counseling are discussed.

Osteogenesis imperfecta is a relatively rare inherited disease of connective tissue affecting skeleton, ligaments, skin, sclera, and dentin. The incidence of this disorder is variably reported to be between 1:20,000 and 1:60,000,[1] with a slight female predominance.

Sillence and coauthors[2] described 4 types of osteogenesis imperfecta based on both inheritance pattern and clinical presentation. These are as follows: Type I is inherited as an autosomal dominant trait and previously has been described as osteogenesis imperfecta tarda, levis form. This type has an onset after infancy and is associated with blue sclerae and fewer fractures. It is the most common variety of the disorder that is of autosomal dominant inheritance. Type II is characterized by an in utero expression of disease, with perinatal death being the commonest outcome. Inheritance is usually autosomal recessive, but in some of these patients with normal parents, the disease may represent a *de novo* mutation. Type III patients have normal sclerae and a progressive bone deformity. Inheritance is autosomal recessive. Type IV is of autosomal dominant inheritance. The patients have normal sclerae and mild expression of disease.

Subsequent researchers have not agreed totally with this classification, and several authors are not convinced that lethal and nonlethal varieties belong to 2 separate entities.[3] Nevertheless, Sillence's 4 types represent a rational basis for understanding the genetic and prognostic heterogeneity of osteogenesis imperfecta.

Two cases of osteogenesis imperfecta are reported in this paper. They show the variety that may exist in expression of the disease, even within a type. One case illustrates an unusual feature—fetal ascites—which has not been reported before in association with osteogenesis imperfecta.

Report of cases

Case 1

A 22-year-old obstetric patient, gravida IV, para I, aborta II, was first referred for ultrasonographic evaluation on January 5, 1984. Ultrasonography revealed a single fetus of approximately 30 weeks' gestation in cephalic presentation. An irregular echo pattern was noted in the skull (Fig. 1). On the basis of this finding, a repeat ultrasonogram in 4 weeks was recommended.

The second study, which was done on February 7, confirmed the irregularity of the echo pattern within the skull and also demonstrated evidence of fetal ascites (Fig. 2). Real time scanning showed the fetal heart beat to be 146 per minute but revealed no fetal movement.

Despite these grave findings, the course of the patient's pregnancy was uneventful and she was seen again on March 6 in early labor. A third ultrasonographic study showed the fetal age to be 38-40 weeks, with the pathologic findings unchanged (Fig. 3). A decision to perform a cesarean section was based on both the fetal skull abnormalities and the history of a previous section

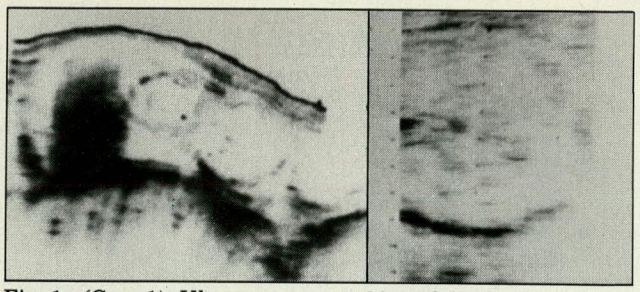


Fig. 1. *(Case 1). Ultrasonogram at 30 weeks' gestation demonstrates poor delineation of fetal head and minimal fetal ascites.*

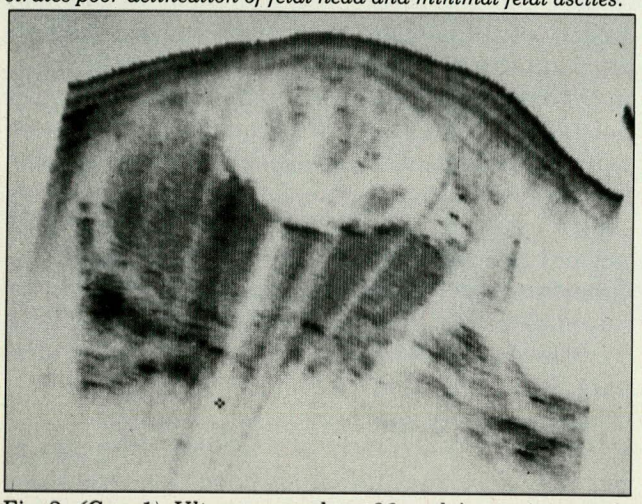


Fig. 2. *(Case 1). Ultrasonography at 36 weeks' gestation reveals fetal ascites.*

with an unknown uterine incision.

On March 7, a small-for-gestational-age, nonviable infant girl was delivered via cesarean section. Physical examination showed a soft, membranous, poorly formed cranial vault and small, misshapen extremities. Postmortem x-ray films revealed multiple fractures and deformities of all long bones, while the cranial vault was poorly calcified and lacked normal osseous structure (Fig. 4).

On autopsy the gross examination revealed multiple abnormalities. The abdomen was extremely distended and appeared to have ascites. The bony plates of the skull were soft, pliable, and abnormally separated from each other, with the parietal plates 2 cm. apart at their closest juncture. The brain showed evidence of polymicrogyria and multiple connective cysts through the white matter. Microscopic tissue examination of the infant's long bones showed a lack of osteoblasts and thin, bony trabeculae with deficient cortex but normal mineralization. The immediate cause of death was intracerebral hemorrhage.

In this case neither parent had any evidence of osteogenesis imperfecta and there was no family history of the disease. The one living child has no evidence of disease and was the product of a normal gestation and delivery. The cause of the patient's two previous first trimester abortions was unknown and probably not related to the current case, because paternal genetics differed in each of the three nonviable pregnancies.

Although the literature suggests that antenatal diagnosis of osteogenesis imperfecta is possible,[1,4] the diagnosis was unsuspected in this case because of the atypical presence of ascites and the inability to detect the long-bone abnormalities prior to delivery. The presence of fetal ascites carries a poor prognosis, with most studies showing 100 percent perinatal mortality associated with it. Ascites is most commonly seen in utero in fetuses affected with urinary tract obstruction, chylous ascites, and multiple anomaly syndromes.[5] It has not been reported previously in association with osteogenesis imperfecta.

Case 2

A 3,289-gram infant boy with an estimated fetal age of 38 weeks was delivered via forceps-assisted vaginal delivery after 14 hours of labor on March 17, 1984. The mother was gravida I, para I, aborta 0, and the child was the product of an uncomplicated pregnancy. The infant's Apgar scores were 6, 7, and 8.

At delivery the infant was noted to have angulation and swelling of the left thigh. Physical examination at this time revealed abnormal triangular facies, blue sclerae, opaque corneas, and cephalhematoma with marked cranial molding. X-rays revealed multiple fractures with involvement of the cranium, left and right clavicles, left radius, and both femora (Fig. 5). Although the x-rays showed no cortical thinning and there was no apparent osteoporosis or bowing of the legs, the physical findings along with the multiple fractures led to a tentative diagnosis of osteogenesis imperfecta, Sillence type II.

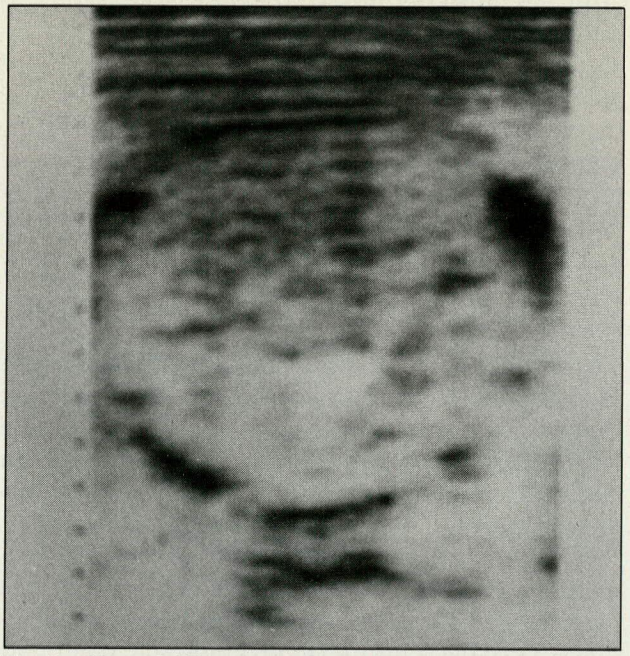
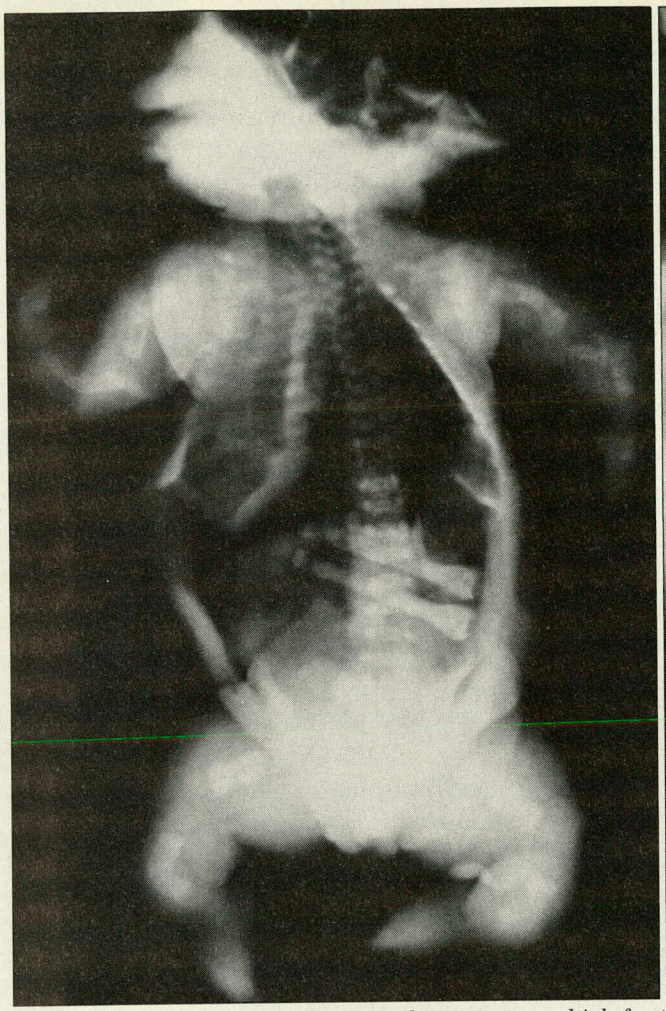


Fig. 3. *(Case 1). Ultrasonogram at 40 weeks' gestation shows poor bony structure of fetal head.*



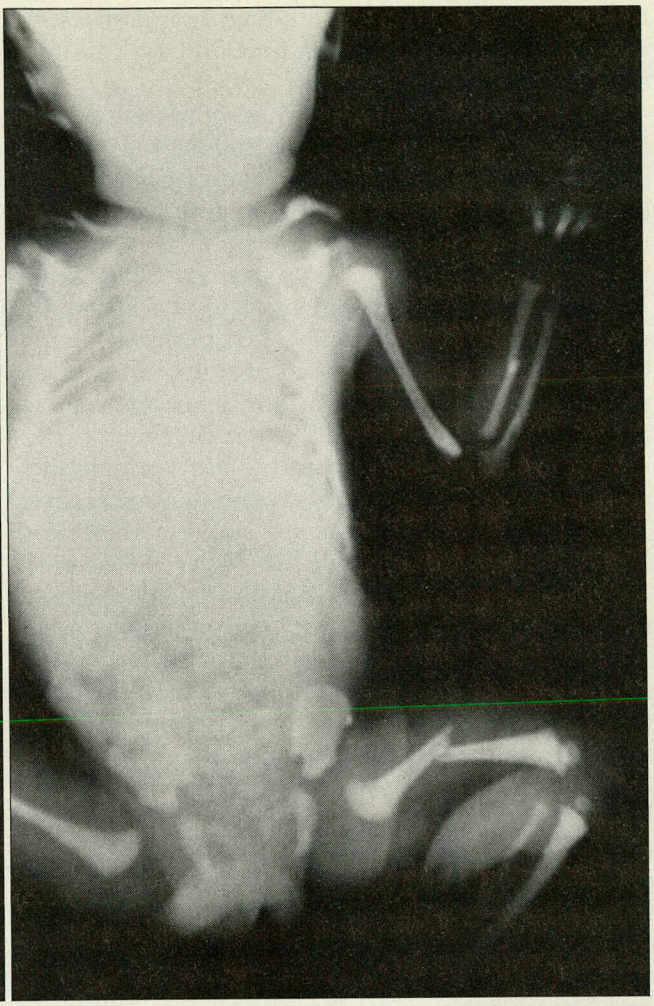


Fig. 4. *(Case 1). Postmortem x-ray view demonstrates multiple fractures at various stages of healing and long-bone deformities.* Fig. 5. *(Case 2). X-ray of viable infant with multiple intrauterine fractures.*

As in the first case, this infant was the product of an outwardly uncomplicated pregnancy, both parents were normal, and there was no history indicative of osteogenesis imperfecta in either parental family.

The question of genetic counseling is a difficult one in this case, because there is little agreement between authorities on the exact genetic pattern of this disease. Older references cite cases such as this, with normal parents and perinatal expression of disease, as evidence of *de novo* mutation with little likelihood of recurrence. In 1979, Sillence and coauthors[2] stated that the vast majority of these type II cases represented an autosomal recessive transmission. In 1982, Spranger and associates[3] challenged previous concepts of inheritance and stated that the separation of the disease into various types with different means of inheritance may be artificial, because both have been seen in the same family.

Review of literature and discussion

Osteogenesis imperfecta is a generalized metabolic disorder associated with blue sclerae, impaired hearing, short stature, poor dentition, hypermobile joints, and abnormal platelet function. Although the pathophysiology remains obscure, there is evidently a defect of collagen maturity related to cross linkages and a hypothetical abnormality in the ATP energy mechanism. Current studies that suggest an abnormality of fibroblast collagen analysis with a deficiency of procollagen type I in relation to type III are presumptive and need to be followed by further research.[6] However, it is now apparent that osteogenesis imperfecta represents a group of diseases with a molecular pathology of collagen. Because of the clinical heterogeneity of the disease, a variety of biochemical lesions may be anticipated.[6] Because the recently described changes in laboratory values (acid phosphatase, amino aciduria, pyrophosphate, glycosaminoglycans, and platelet and thyroid functions)

remain unconfirmed, the diagnosis is presently made on clinical findings and family history alone.[7]

Clinically there is a wide range of presentation, and currently no clear-cut prognostic indicators are available. The patient who at an early age has blue sclerae, delayed walking, and multiple fractures may eventually have a less severe course than the preschooler who only has leg bowing and 1 or 2 fractures. Indeed, Moorefield and Miller's[8] excellent retrospective study of 31 patients found that the severity of disease was unrelated to scleral tint, age at onset, or family history. The 2 most accurate prognostic indicators in their study were the amount of preoperative leg bowing and, radiologically, the degree of diaphyseal tapering.

Classic physical findings associated with osteogenesis imperfecta include blue sclerae, stature less than the fifth percentile, scoliosis, and craniofacial dysproportion with triangular facies and "helmet head" configuration of the skull. Bone fragility is the most outstanding feature of the disease, and fractures often occur in response to minor trauma. In the severe congenital form, over 100 fractures may be present at birth. The lower limbs are more frequently fractured. In these patients a bone that has been fractured once tends to do so repeatedly because of angulation of the fragments and disuse atrophy secondary to immobilization. Fracture healing appears to proceed at a normal rate, but the resultant callus can be large and hyperplastic, mimicking osteogenic sarcoma on x-ray. Osteogenesis imperfecta patients are at particular risk for fracture complications such as pseudoarthrosis, deformity due to angulation, and growth arrest after epiphyseal plate fractures.

The patients are very vulnerable to respiratory distress, and a major cause of death is respiratory insufficiency. This may be due to inadequate rib stability in infants, fractures due to coughing in older children, or infection superimposed on a lung compromised by kyphosis and scoliosis in an adolescent.[7]

In addition to the clinical findings associated with their osseous defects, the patients often have other connective tissue-related findings. Frequently the musculature is hypotonic and the skin is thinned with a tendency toward subcutaneous bleeding. Dentinogenesis imperfecta, characterized by teeth that are deficient in dentin, easily broken, and especially susceptible to caries, can be an isolated finding. Deafness, which does not appear as common as earlier reported, may occur in early adulthood or adolescence and can be either conduction (osteosclerosis) or nerve (due to pressure of the helmet-head cranial bones on the eighth cranial nerve as it emerges from the skull) type.

Typical radiologic findings of osteogenesis imperfecta are multiple fractures in various stages of healing, deficient cortex (mainly seen in long bones), and very osteoporotic bones. Examination of the skull may be very helpful, because it usually has a very typical "mushroom" appearance with a broad forehead. In addition, the presence of "significant wormian bones" (which one study defined as more than 10 bones measuring greater than 6 mm. by 4 mm. showing a mosaic pattern)[9]in a patient with other suggestive findings may provide the key to diagnosis.

In general the differential diagnosis includes various rare osteodysostoses and will vary according to the age and presentation of the patient. Two pitfalls which should be considered are long-term steroid use and child abuse. Both of these can produce a radiographic picture highly suggestive of osteogenesis imperfecta and vice-versa.

Management of the patient with osteogenesis imperfecta of necessity focuses on fracture care. Unfortunately, at this time no proved effective pharmacologic treatment is available.[7] A review of past protocols shows that over 20 different treatments have been tried using agents as varied as aluminum, arsenic, estrogen, diet, thyroid, and calcitonin; all are without verifiable effect.[10]

Current articles recommend the attitude that these patients are handicapped, not sick, and that all treatment goals should be based on adult needs for mobility.[7] With the recognition that osteoporosis due to immobilization is superimposed on the basic collagen defect, fracture care becomes more aggressive, with the goal being early weight bearing to increase stress on the bones and decrease osteoporosis. Fortunately, the rate of fractures diminishes dramatically after puberty. In a study reported by Moorefield and Miller,[8] a group of patients sustained an average of 31 fractures each, with 91 percent of these occurring before puberty; the average postpubescent number was 4.2 fractures. Currently, the decrease in fracture rate is felt to be related to the action of the sex steroids on the skeleton.

With these goals of mobility in mind, plastic orthoses are used for compression of the incompressible fluid muscle mass around the bone. To facilitate early weight bearing, movable gantries, which bear part of the rehabilitating patients' weight, are used.[11] In addition, surgical treatment by multiple osteotomy and intramedullary rod fixation improves long-bone deformity and enhances the potential for ambulation with small risk of complication.[8] Kyphosis and scoliosis remain seri-

ous causes of morbidity and mortality, with the incidence of scoliosis approaching 90 percent in adolescents and adults with this disease.[7] Brace treatment is ill advised in these patients because it often leads to progressive rib deformity. Operative correction with metal supports is filled with complications and also must be undertaken with care.

In spite of a deforming, debilitative disease and multiple surgical procedures, patients with osteogenesis imperfecta generally adapt extremely well both socially and psychologically to their disabilities. Several studies have commented on the high intelligence and extroversion of these patients and their ability to become productive members of society.[7]

Comment

The first case reported here represents a previously unreported finding of fetal ascites in what was subsequently diagnosed as osteogenesis imperfecta type II. Although fetal ascites is associated with multiple fetal anomaly syndromes, osteogenesis imperfecta represents a single disorder of connective tissue with multiple forms of expression. It has not been reported to be associated with other fetal anomalies. The diagnosis in this case could probably have been ascertained positively prior to delivery by the use of amniocentesis and analysis of skin cell fibroblast collagen;[4] however, because the patient's pregnancy was in the thirtieth week at the time of the first ultrasonogram and the treatment of her condition would not have been altered, such studies were not performed.

The cases reported here provide ample evidence that the clinical and genetic variety displayed by osteogenesis imperfecta make both genetic counseling and establishment of a prognosis problematic. Despite extensive research, there continues to be no reliably reproducible laboratory test to establish the diagnosis and no clinically proved treatment protocol. Despite these handicaps many patients with this disease respond well to fracture treatment with external orthosis and intramedullary rodding. The incidence of fractures decreases after puberty for reasons essentially unknown at this time, and the majority of these patients who survive to adulthood become handicapped but functional and productive members of society.

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