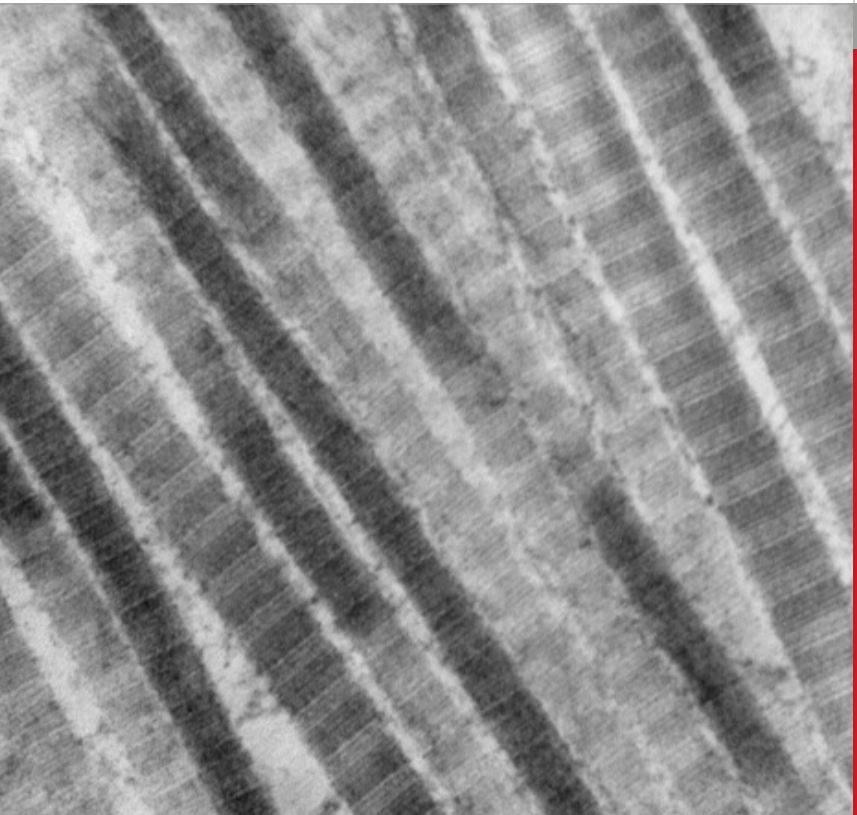
SWISS SOCIETY OF NEONATOLOGY

A severe case of osteogenesis imperfecta



October 2016

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Title figure:
TEM image of collagen fibres (source: www.wikipedia.org)

Osteogenesis imperfecta (OI), also known as «brittle bone disease», is a group of inherited connective tissue disorders with heterogeneous phenotypic manifestations. It qualifies as an orphan disease, with an estimated prevalence of 6 – 7 per 100'000 (1). Mutations in one of two genes coding for the α1(I) and α2(I) chains of type I collagen (COL1A1 and COL1A2, respectively), are responsible for most cases and cause bone fragility, low bone mass and extra-skeletal manifestations such as dentinogenesis imperfecta and hearing loss. Disease severity depends on the effect of the specific mutation and ranges from premature osteoporosis in mild forms to perinatal death in the worst forms (1– 4). The significant clinical and genetic heterogeneity has led to different classification systems. Most recently, Forlini et al categorized OI into five functional metabolic groups (A: defects in collagen synthesis, structure or processing; B: defects in collagen modification; C) defects in collagen folding and cross-linking; D: defects in bone mineralization; E: defects in osteoblast development with collagen insufficiency) (4 – 6).

Patients with OI requires a multidisciplinary treatment approach. Pharmacological therapy with bisphosphonates is associated with significant improvements in bone mineral density but no major reduction in fractures (1, 7, 8).

This female infant was born to a healthy 20-year-old G2/P2 by Cesarean section at 38 1/7 weeks. Prenatal ultrasounds at 14, 17 and 20 weeks' gestational age had shown short long bones (lengths below the 5th percentile) and bent femurs; fractures could not be excluded at that time. The spectrum of differential diagnoses including various forms of skeletal dysplasias was discussed with the parents. To exclude thanatophoric dysplasia, chorionic villus sampling was performed and a mutation in the fibroblast growth factor receptor 3 (FGFR3) was excluded. Family history was unremarkable and there was no consanguinity.

The girl adapted well with Apgar scores of 5, 7 and 9 at 1, 5 and 10 minutes, respectively. Umbilical venous cord-pH was 7.35. Her birth weight was 2300 g (< P3, -2.2z), length 34 cm (< P3, -7.6z) and head circumference 34 cm (P45, -0.2z). Due to signs of respiratory distress immediately after birth, respiratory support by nasal CPAP was started with a maximal fraction of inspired oxygen of 0.3. An umbilical venous catheter was placed before transfer to the NICU.

On clinical examination, severe short stature, short and deformed limbs with thick skin folds, a triangular and hypoplastic midface, a short neck and a shortened, wide thorax were noted (Fig. 1). In addition, sclerae with a bluish tint and a soft skull with large fontanels suggesting incomplete ossification were observed.

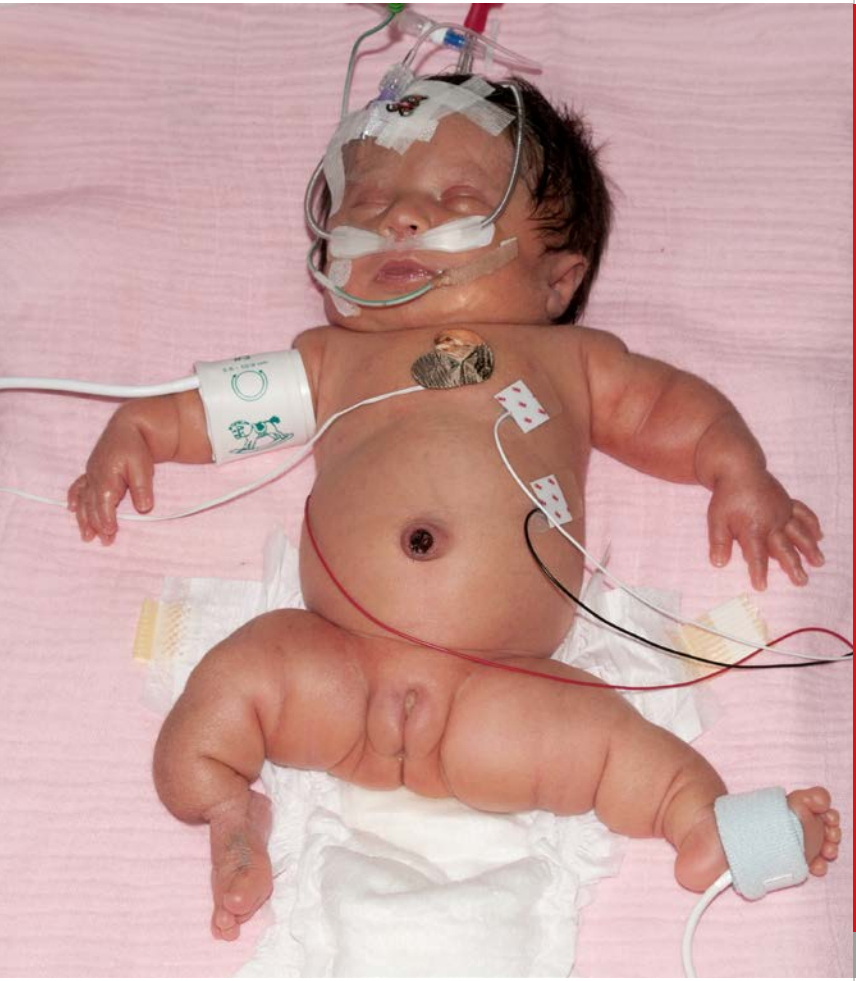

Fig. 1

Clinical appearance of the patient in the first week of life: short stature, deformed extremities with thick skin folds.

X-rays showed multiple fractures of the limbs, ribs, and clavicular callus formation. Additionally, reduced height of some vertebral bodies (platyspondyly), especially from T11 to L1, was noticed (Fig. 2, 3). There was dorsal flattening of the skull, and sintering of the cervical vertebrae C2 and C3 was noticed (Fig. 4). Because an unstable fracture in this region as well as at the cervico-occipital connection could not be excluded, computer tomography was performed showing an old non-dislocated fracture of the axis with callus formation. On all X-rays pronounced osteopenia was noticed. Since ultrasound examination of the hips was difficult, suspected hip luxation was confirmed by magnetic resonance imaging.

Nasal CPAP could rapidly be weaned and was discontinued on day of life (DOL) 2. However, on DOL 4, when recurrent apnea occurred and respiratory distress reappeared, therapy with high flow nasal cannula and oxygen supplementation was initiated and amoxicillin/clavulanic acid and amikacin were started because of suspected omphalitis. At the same time, echocardiography showed signs of pulmonary hypertension without structural or functional cardiac anomalies.

Therapy with acetaminophen and morphine followed by methadone was initiated right after birth to treat pain associated with multiple fractures. Nursing care of the girl was optimized by a multidisciplinary approach with participation from the neonatology team, physio-

therapists, orthopedic and rheumatology specialists.

After extended discussions with the parents, pharmacological therapy with bisphosphonates was started. On DOL 5, the first intravenous dose of neridronate (1 mg/kg) was given without complications and repeated after 24 hours. A second treatment cycle was administered seven weeks later.

On DOL 30, when the girl's respiratory condition deteriorated again, she was intubated and invasive mechanical ventilation was started. She received antibiotics for suspected pneumonia for 10 days. At this point, an interdisciplinary ethical case conference was organized and it was decided not to reintubate in case of extubation failure and to forgo cardiac resuscitation attempts in case of a cardiac arrest.

After two weeks of mechanical ventilation she was successfully extubated to high flow nasal cannula therapy. Over the next few weeks, she could be weaned from non-invasive respiratory support and was discharged home with specialized homecare at the age of three months. However, she was readmitted only one day later because of fever and respiratory distress. At this point, it was agreed to initiate comfort care. The patient died of respiratory failure a few days later.

Biochemical analysis of collagens on cultured skin fibroblasts by SDS-PAGE and fluorography revealed

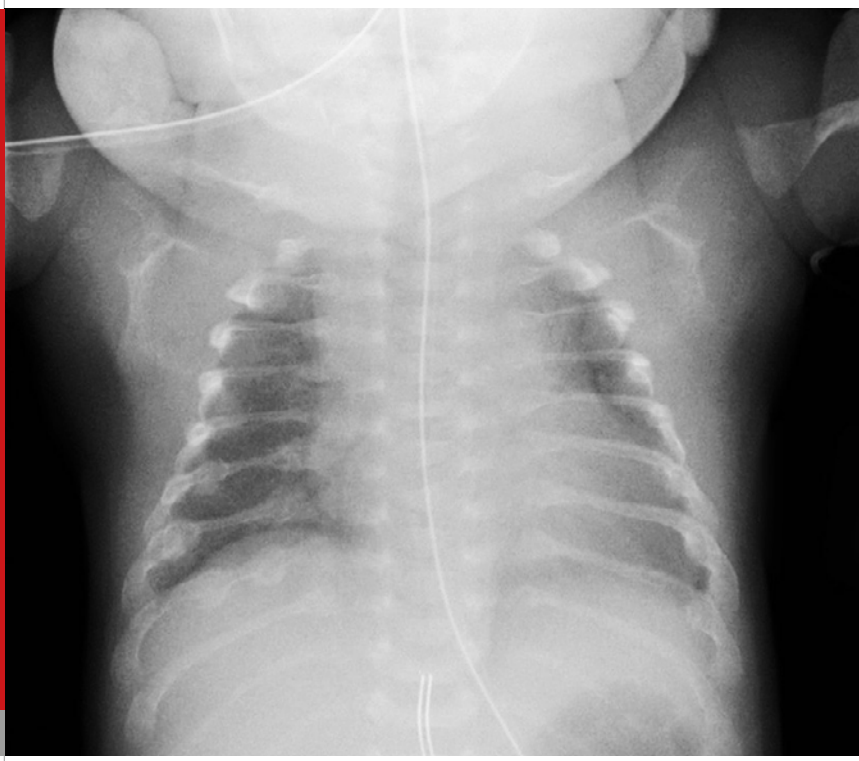

Fig. 2

Chest X-ray: multiple bilateral rib fractures with some callus formation, small thorax, intrahepatic position of the umbilical venous catheter.

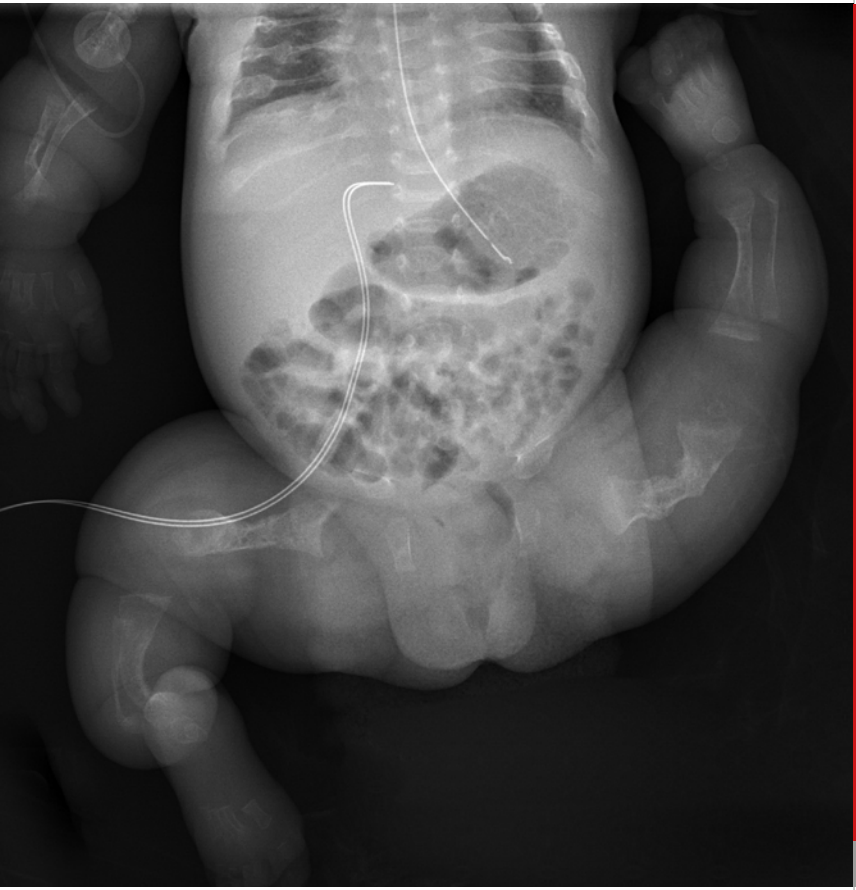

Fig. 3

Abdominal X-ray: multiple fractures of long bones with deformation, fractured ribs, reduced height of vertebral bodies T11 to L1 (platyspondyly), mal-positioned umbilical venous catheter.

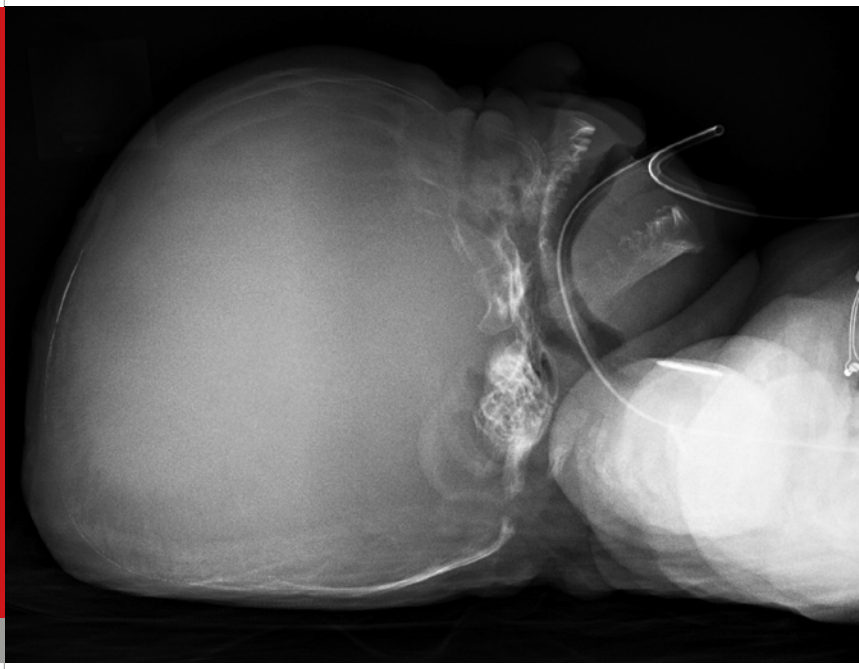

Fig. 4

Skull X-ray (lateral view): dorsal flattening of the skull with marked osteopenia, sintering of C2 and C3.

abnormal collagen type α1(I) and α2(I). Genetic testing of COL1A1 and COL1A2 genes using next-generation sequencing revealed a heterozygous variant (c.2326G>C, p.Gly776Arg) in the COL1A1 gene. This novel mutation leads to the exchange of a highly conserved amino acid and is predicted to be pathogenic, thus confirming the clinical diagnosis. A different mutation in the same amino acid position (Gly776Ser) has previously been described to be pathogenic (1,3). Parents opted against further parental testing.

DISCUSSION

This case report describes the clinical course of an infant with an early lethal form of OI. Table 1 shows the classical clinical classification of COL1A1/2-related OI proposed by Sillence in 1979; this system is still helpful in providing information about prognosis and management of the disease (5, 6). Based on clinical, radiographic and genetic findings, the disorder in our patient was classified as Sillence type II. According to the most recent classification of OI mentioned above, our case belongs to group A with a primary defect in collagen structure and processing (4).

Infants with OI type II usually die within a few hours or days after birth due to respiratory failure related to a small thorax and poor thoracic compliance due to multiple rib fractures (8, 9). Our patient died of respiratory failure at the age of four months, which is unusually late for this form of OI. The prolonged clinical course suggests that the skeletal deformities were not the only cause of respiratory failure that lead to the death of the patient.

Initially, our patient required non-invasive respiratory support for a few days because of transient pulmonary hypertension. The secondary respiratory deterioration was possibly related to intrinsic collagen-related abnormalities of the lung tissue and respiratory tract infection. Data obtained from studies in mouse models as well as from OI patients have demonstrated downregulation of COL1A1 transcripts in lung tissue

Type	Severity	Fractures	Bone deformity	Stature	Sclerae
Type I: classic non-deforming OI with blue sclerae	Mild	Few to 100	Uncommon	Normal or slightly short for family	Blue
Type II: perinatally lethal OI	Lethal in perinatal period	Multiple fractures of ribs, minimal calvarial mineralization, platyspondyly, marked compression of long bones	Severe	Severely short stature	Dark blue
Type III: progressively deforming OI	Severe	Thin ribs, platyspondyly, thin gracile bones with many fractures, «popcorn» epiphyses common	Moderate to severe	Very short	Blue
Type IV: common variable OI with normal sclerae	Mild to moderate	Multiple	Mild to moderate	Variably short stature	Normal to grey

Table 1. *Sillence classification and clinical features of classical COL1A1/2-related osteogenesis imperfecta (1,5).*

leading to loss of extracellular matrix integrity which may contribute to respiratory failure (10, 11).

To the best of our knowledge, therapy with intravenous bisphosphonates at the age of one week of life has not yet been described. The observation that bisphosphonates increase bone mineral density and possibly reduce bone pain in children below three years of age suggests that this treatment should be started as early as possible. Compared to adults, the duration of the beneficial treatment effect is shorter in children; therefore, the treatment with bisphosphonates should be repeated every two months (1, 7, 12, 13). In our patient, neridronate was administered primarily with the aim of reducing bone pain; data on fracture rate reduction is still scarce. We used neridronate instead of pamidronate because it is the only bisphosphonate registered for treatment of OI in children in Europe. It can be administered as a single intravenous dose; however, because of the commonly described influenza-like reactions after the first administration of bisphosphonates, the initial infusion was divided into two doses (8, 14).

Acknowledgements

Genetic testing of COL1A1 and COL1A2 was performed by the Institute of Medical Genetics at the University of Zurich. The authors would like to acknowledge the nursing team for their tender care of the patient.

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