Case Report

Perinatal Lethal Osteogenesis Imperfecta in a Thai Newborn: The Autopsy and Histopathological Findings

Wanwisa Himakhun MD*,
Kitiwan Rojnueangnit MD**, Sariya Prachukthum MD**

* Department of Pathology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand
** Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani, Thailand

Osteogenesis imperfecta (OI) is an inherited disorder of type I collagen synthesis with an estimate incidence of 1 in 100,000 live births. Among all types, OI type II is the most severe type with perinatal death. The authors describes a male neonate with characteristic features of osteogenesis imperfect type II, including short crumpling limbs, beaded ribs, poorly bony ossification and blue sclera. Autopsy with histological study revealed not only multiple fractures, but pulmonary hypoplasia and intracerebral hemorrhages were also present. Both are the leading causes of death in the lethal type OI patients.

Keywords: Osteogenesis imperfect, Fracture, Intracerebral hemorrhage

Case Report

A preterm newly born male infant was the first child of non-consanguineous parents. The parents were 28 years old and phenotypic normal. His primigravida mother had not received prenatal care and she came to the hospital because of labor pain. He was born at 34 weeks’ gestation by cesarean section due to fetal distress. The Apgar scores were 3 and 7 at 1 and 5 minutes, respectively. He developed respiratory distress at birth that required endotracheal intubation and ventilator support. He was admitted to the neonatal intensive care unit.

On physical examination, he was a disproportionately grown and short stature infant, his weight was 1,515 g (-2 SD), length was 34 cm (< -2 SD) and head circumference was 28 cm (-2 SD). He had dysmorphic features including soft calvarium, shallow orbits and blue sclera. Deformed and short limbs, small thorax, multiple ribs and long bones fractures with platyspondyly of vertebrae were noted in the radiography (Fig. 1B).

He had tachypnea and retraction with no improvement from ventilator support. His vital signs were in normal range except for his respiratory rate is 70-100/min, until the sixth day after birth, he died of respiratory failure. An autopsy was performed.

Autopsy findings

The body was that of a male newborn whose body weight was 2,500 grams. The crown-heel length was 34 cm. Both upper and lower extremities appeared short and depressed. Right indirect inguinal hernia was present. The head was soft corresponded to poorly ossified calvarium by the radiograph (Fig. 1A, 1B). Both sclerae were deep grey-blue. The so-called “beaded ribs”, crumpling femurs, marked long bone deformity and platyspondyly spine (Fig. 1A, 1B) were noted.
Histological sections from the rib (Fig. 2B) revealed irregularity of osteocartilaginous junction with paucity of bone-trabeculae of primary and secondary spongiosa. The cortex was markedly thin and multifoci of disruption due to previous fracture were noted. There was an inguinal hernia in the right groin containing part of duodenum, ileum and ascending colon but no gangrene or peritonitis was present. The heart was normal in size and shape. A ductus arteriosus measuring 0.2 cm in diameter was observed connecting the aorta and pulmonary trunk. Bilateral lungs showed immaturity and “pulmonary hypoplasia” (A ratio between lungs and body weight was less than 0.012 for fetus with gestational age of more than 28 week). The histopathology of lungs showed hyaline membrane, pulmonary congestion and edema (Fig. 3A, 3B). The calvariums were soft and appeared semi-translucent which corresponded with the paucity of bone formations in the process of membranous ossification in the skull by histological examination. Dark-red areas on bilateral temporal represented focal areas of hemorrhages in the calvarium (Fig. 4A, B). Diffuse subarachnoid and intraventricular hemorrhage were noted in the right temporo-parietal area (Fig. 5A).

Discussion

The case showed osteopenia and multiple fractures during intrauterine period, bone as shown by
x-ray and confirmed by pathologic findings. Blue sclera was also found and fulfilled the criteria for perinatal lethal form of OI as shown in Table 1 and 2.

Previously, osteogenesis imperfecta (OI) was classified into 4 types, type I-IV according to Sillence classification which based on only clinical features and genetic defects regarding production of collagen type I(5). Nowadays, OI is classified into 9 types based on mode of inherited, clinical findings, histological features and mutated gene regarding not only collagen production but also included the production of some other extracellular substances as summarized in Table 2. The severity increasing from type I < types IV, V, VI, VII < type III < types VIII, IX < type II(5,6). From clinical consideration per se, perinatal lethal form may be classified as type IIA (MIM 166210), COL1A1 or COL1A2 mutation, which was found in most cases or types IIB (MIM610854), VIII (MIM 610915) or IX (MIM 259440) of which mutated gene CRTAP, LEPRE1 or PPIB were identified in 5% of cases(7,8).

Perinatal lethal OI or OI type II was also divided into 3 groups based on radiological subclassification; II-A which is characterized by broad ribs with multiple fractures, continuous beaded ribs and severe under-modeling femur, II-B by normal or thin ribs and discontinuous beaded ribs and II-C by varying thickness of ribs, discontinuous beaded ribs and slender twisted long bones(9). According to Sillence Classification, our case should be classified as OI type IIA because of the findings of short, beaded ribs, crumpled long bone due to multiple fractures and poor bone remodeling(10-12).

The prevalence of OI is 6-7/100,000. Mild form (type I and IV) is found more than half of cases and incidence of OI type II is 1-2/100,000 but now it may be less due to early prenatal recognition(3). Perinatal lethal OI can be recognized earliest in 12-13 weeks’ gestation by prenatal ultrasound; the accuracy ranged from 34-65%(13-15).

The cause of death in the case should be due to: firstly, pulmonary hypoplasia with respiratory failure that related to multiple intrauterine rib fractures causing limitation of lung expansion(16,17); secondly, intracerebral hemorrhage which might occur due to birth injury(11) or even spontaneous bleeding by vascular collagen defect in non-lethal types of OI(18,19). This case was born by caesarean section without evidence of head injury plus the stable blood pressure during admission time, so spontaneous intracerebral hemorrhage was more-likely.

We did not have molecular study for this case due to unavailable facility. However, most of perinatal lethal OI showed mutation of COL1A1&2 genes and transmitted as autosomal dominant inheritance and approximately 5-9% of cases showed germline

Table 1. Skeletal disorders in differential diagnosis with perinatal lethal OI

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Bone fragility plus</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruck syndrome (osteogenesis imperfecta with congenital joint contractures)</td>
<td>Joint contractures</td>
<td>Defects in lysyl hydroxylase (crosslink formation), AR inheritance</td>
</tr>
<tr>
<td>Osteoporosis pseudoglioma syndrome (ocular form of osteogenesis imperfect)</td>
<td>Blindness in infancy</td>
<td>Mutations in lipoprotein receptor-related protein-5 gene, AR inheritance</td>
</tr>
<tr>
<td>Hypophosphatasia, perinatal type</td>
<td>Low bone turnover and low serum alkaline phosphatase</td>
<td>mutation in the gene encoding tissue-non specific alkaline phosphatase (ALPL), AR inheritance</td>
</tr>
<tr>
<td>Cole-Carpenter syndrome</td>
<td>Craniosynostosis and hydrocephalus</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Modified from references(2,3)
Table 2. Summarized new classification of OI

<table>
<thead>
<tr>
<th>Type</th>
<th>Severity</th>
<th>Clinical features</th>
<th>DI</th>
<th>sclera</th>
<th>Mode of inheritance</th>
<th>Mutated gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild</td>
<td>Normal height or slightly short, few to 100 fractures, no bone deformity, wormian skull, codfish vertebrae, progressive hearing loss (50% in adult)</td>
<td>rare</td>
<td>blue</td>
<td>AD</td>
<td>COL1A1</td>
</tr>
<tr>
<td>IIA</td>
<td>Lethal</td>
<td>Multiple ribs and long bone fractures, small beaded ribs, short stature, severe deformity, minimal calvarial mineralization, platyspondyly vertebrae</td>
<td>-</td>
<td>dark blue</td>
<td>AD</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>IIB</td>
<td>Same as IIA</td>
<td></td>
<td></td>
<td></td>
<td>AR</td>
<td>CRTAP</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>Very short stature, triangular face, severe scoliosis, marked bone deformity, flared metaphyses, severe osteoporosis</td>
<td>+</td>
<td>Gray/ blue</td>
<td>AD, rare AR</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate</td>
<td>Moderately short, mild to moderate scoliosis, thin ribs, protrusia acetabuli</td>
<td>+/-</td>
<td>White/ gray</td>
<td>AD</td>
<td>COL1A1 or COL1A2</td>
</tr>
<tr>
<td>V</td>
<td>Moderate</td>
<td>Mildly to moderately short, multiple with hypertrophic callus</td>
<td>No</td>
<td>White</td>
<td>AD</td>
<td>Unknown</td>
</tr>
<tr>
<td>VI</td>
<td>Moderate to severe</td>
<td>Moderately short, Rhizomelic shortening</td>
<td>No</td>
<td>White</td>
<td>Uncertain</td>
<td>Unknown</td>
</tr>
<tr>
<td>VII</td>
<td>Moderate</td>
<td>Mildly short</td>
<td>No</td>
<td>White</td>
<td>AR</td>
<td>CRTAP</td>
</tr>
<tr>
<td>VIII</td>
<td>Severe to lethal</td>
<td>Severe deformity to perinatal lethal</td>
<td>-</td>
<td>White</td>
<td>AR</td>
<td>LEPRE1</td>
</tr>
<tr>
<td>IX</td>
<td>Severe to lethal</td>
<td>Similar to type II-III</td>
<td>+/-</td>
<td>Blue/white</td>
<td>AD</td>
<td>PPIB</td>
</tr>
</tbody>
</table>

Modified from references (1-3,6,12)

mosaicism; Only few cases of AR inherited perinatal OI, the recurrent risk is up to 25% in the couples who are both carriers (11,20).

Acknowledgement
The authors would like to thank Prof. Vorachai Sirikulchayananta and Prof. Duangrudee Wattanasirichikoon for revision of the content and Mr. Santigo Dino for the written English of this manuscript.

Potential conflicts of interest
None.

References


ลักษณะความผิดปกติทางพยาธิวิทยาจากการตรวจศพในทางกาย 1 ราย ที่เป็นโรคกระดูกเปราะ กรรมพันธุ์

วันวิสาข์ หิมะคุณ, กิติวรรณ โรจนเนืองนิตย์, ศริยา ประจักษ์ธรรม

โรคกระดูกเปราะกรรมพันธุ์ (osteogenesis imperfecta; OI) เป็นโรคทางพันธุกรรม ซึ่งมีสาเหตุจากความผิดปกติของการสังเคราะห์ ทดสอบทางปฐมวัย 1 พบครั้งละประมาณ 1 ใน 100,000 ของয়


ลักษณะความผิดปกติทางพยาธิวิทยาจากการตรวจศพในทางกาย 1 ราย ที่เป็นโรคกระดูกเปราะ กรรมพันธุ์

วันวิสาข์ หิมะคุณ, กิติวรรณ โรจนเนืองนิตย์, ศริยา ประจักษ์ธรรม

โรคกระดูกเปราะกรรมพันธุ์ (osteogenesis imperfecta; OI) เป็นโรคทางพันธุกรรม ซึ่งมีสาเหตุจากความผิดปกติของการสังเคราะห์ ทดสอบทางปฐมวัย 1 พบครั้งละประมาณ 1 ใน 100,000 ของโรคภูมิคุ้มกัน มีลักษณะที่เป็นโรคกระดูกเปราะกรรมพันธุ์ ประเภทที่ 2 จัดเป็นกลุ่มที่มีความรุนแรงของการถูกสูญเสียของโรคมากที่สุด และมักเสียชีวิต ตั้งแต่ก่อนเกิด มีการระลึกถึงความผิดปกติทางกายภาพ 1 ราย ซึ่งมีลักษณะทางคลินิกซึ่งเกี่ยวกับโรคกระดูกเปราะกรรมพันธุ์ คือ เทาน้ำและน้ำเกลือ กระดูกซึ่งมีรอยแตกซ้ำกันเล็กน้อย พบการสร้างกระดูกมาก ซึ่งมีการต่อกันอย่างไม่สม่ำเสมอ แล้วมีการระลึกถึงความผิดปกติทางระบบประสาทและมีการต่อกันอย่างไม่สม่ำเสมอ ซึ่งเป็นสาเหตุหลักของการเสียชีวิตที่พบได้บ่อยที่สุดในผู้ป่วยที่เป็นโรคภูมิคุ้มกัน