REVIEW ARTICLE

Recent progress in osteogenesis imperfecta

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Osteogenesis imperfecta (OI), a rare clinical disease with abnormal type I collagen, is inherited or caused by mutation. A classification of OI into four types was proposed in 1979 and has been used up until four new types were added recently. A tough clinical challenge, OI causes abnormal blood coagulation and cardiovascular structure, airways obstruction, and delayed wound healing. The authors of the current article have reviewed recent progress in OI worldwide, including the mechanisms, classification, detection, clinical difficulties, and treatment.

Key words: Collagen type I; Diphosphates; Osteogenesis imperfecta; Stem cell transplantation

Introduction

Osteogenesis imperfecta (OI) is a rare clinical disease, occurring at a rate of between 1/10,000 and 1/25,000 worldwide¹. There are currently very few published articles about OI in China and most of them are merely single case reports. Lack of a good understanding of difficulties in the diagnosis, optimal treatment, and recent progress about this disease in the world could potentially result in problems for physicians, such as missed diagnosis, diagnostic error, or litigation. The authors of the current article have reviewed recently published articles about OI, in order to improve understanding of this disease.

Molecular and biological changes

Osteogenesis imperfecta is a connective tissue disease with abnormal type I collagen which is inherited or caused by mutation. The clinical symptoms vary and include multiple fractures, blue sclerae, advancing deafness, beading of the ribs, osteoporosis, and deformity of the skull. Type I collagen is a triple helix structure consisting of two $\alpha 1$ chains and one $\alpha 2$ chain. The $\alpha 1$ chain is controlled by the COL1A1 gene in the 17th chromosome and the $\alpha 2$ chain is controlled by the COL1A2 gene in the 7th chromosome. Any changes in these two genes will lead to abnormalities of type I collagen. Further molecular biology studies have found that the two chains have

repeated glycine-proline-hydroxyproline dextrorotated triplet structures. This triplet structure is extremely important for the correct folding of the peptide chain. Abnormality in this triplet, caused by gene changes, leads to incorrect alignment of the peptide and eventually to abnormal type I collagen².

Additionally, it is thought that cartilage-associated protein (CRTAP), prolyl3-hydroxylase 1 (P3H1/LEPRE1) and cyclophilin B (CyPB/PPIB) also influence this triplet structure, and may be involved in the pathogenesis of OI.

Classification

The earliest OI classification was reported by Sillence in 1979³. This author divided the disease into four types (types I to IV). This classification has been used until recently, when four new types were added (types V to VIII)¹.

Type I, the mildest, is manifested by osteoporosis, multiple fractures, and blue sclerae. Fractures are common in the neonatal period, but rare in the uterus or after adulthood has been reached.

Type II is the most severe type, most cases dying before, or shortly after, birth. Severe osteoporosis, poor mineralization, beading of ribs, shortening of the long bones, and multiple fractures occur in this type.

Type III is milder than type II, but the most serious type in which affected children survive past infancy. Blue sclerae are rare in this type, but the incidence of fracture and clinical severity increase with time and only rare cases survive into adulthood.

Type IV patients do not have blue sclerae, but the rest of their clinical symptoms are similar to type I. However shortening of the long bones is more obvious after adulthood has been reached.

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Received: 3 January 2011; accepted 25 January 2011

DOI: 10.1111/j.1757-7861.2011.00128.x

The gene changes in types V and VI are obscure. A feature of type V is hypertrophic bony callus after trauma or surgery, which needs to be distinguished from chondrosarcoma. In addition the interosseous membrane in this type tends to develop calcification with secondary dislocation of the head of the radius and limited rotation ability. The characteristic of type VI is a defect in mineralization of cartilage.

Types VII and VIII are thought to be related to CRTAP and the LEPRE1 gene. Type VII patients tend to have skeletal abnormalities and brittle bones, and type VIII patients have defects in growth and mineralization.

Detection methods

Routine prenatal screening by ultrasound or genetic testing can achieve good results for patients with positive family histories. However the detection rate is very low where there is no family history, which can lead to missed diagnosis, diagnostic error, or litigation. Physicians should have a high index of suspicion for such cases.

Ultrasound

Being a non-invasive method, ultrasound is the main prenatal screening method. Most cases diagnosed prenatally by ultrasound are type II, with fewer cases of type III. This is because types I and IV can be normal before birth, and types V to VIII are extremely rare in clinical practice^{4,5}. Abnormalities found include reduced echoes, shortening of the bones, angulations, changes in curvature, multiple fractures, and beading of the ribs. Discontinuity of bone can also cause a wrinkly appearance^{5,6}. Transvaginal ultrasound can detect abnormality at the 14th week, whereas transabdominal ultrasound can detect abnormality only after the 15th or 16th week⁷. This technique requires a highly experienced operator. In families with a prior abnormal child, this technique is reliable; otherwise it is still easy to miss the diagnosis⁴.

Collagen analysis and genetic testing

Skin biopsy used to be the main method of diagnosing OI. However this method took a long time (several weeks) and had poor accuracy. Wenstrup *et al.* analyzed 132 cases of OI and found the false negative rate was as high as 13.2%⁸. Now, combined skin biopsy and DNA sequence testing are recommended to make the diagnosis. Some researchers have reported the use of chorionic biopsy under ultrasound guidance combined with DNA sequence testing for diagnosing OI. This method can make the diagnosis at the 14th week. However it is invasive and can cause injury to the infant or result in premature delivery.

The reliability of genetic testing has relied on the development of new techniques. Van Dijk *et al.* compared two techniques in 106 cases of mild OI⁹. The first technique used electrophoresis of type I collagen protein combined with a COL1A1/2 gene sequence test. The latter used multiplex ligation-dependent probe amplification (MLPA). They found that MLPA was the superior and more reliable method for finding genetic abnormalities.

Radiography of the uterus

Radiography of the uterus can be used when ultrasound and genetic testing have failed to diagnose strongly suspected cases. Besides the common changes of OI, this technique can detect the Wormian bone, a single skull bone surrounded by sutures. When the number of Wormian bones is greater than 10, this is considered to be a significant number of Wormian bone (SNWB) and OI is highly likely⁷. Semler *et al.* used radiography on 195 OI cases (types I, III, and IV)¹⁰. They found the incidence of SNWB in each type to be 35%, 96%, and 78%, respectively. They therefore declared that SNWB tends to appear in severe cases and can be a reliable tool for diagnosis. However this method can cause radiation injury. In addition, fetal movement and overlapping of fetal bones with the mother's bones can obscure the diagnosis¹¹.

Clinical challenges

Abnormal blood coagulation

Edge *et al.* have reported that OI cases have increased vascular fragility, reduced clotting factor VIII and abnormal platelet function¹². It is necessary to regularly check coagulation function and platelet counts. Even in cases with normal coagulation, post-operative bleeding is possible. If the platelet count is less than $20,000 \times 10^9/L$, blood transfusion is needed and fresh blood containing all of the clotting factors is the best choice¹³.

Airways obstruction

The strength of the chest muscles is weak in patients with OI. In the late phase of surgical anesthesia, the respiratory muscles have difficulty compensating and airways obstruction is likely to occur¹². In such cases, delayed extubation is necessary and corticosteroids can reduce local edema.

Abnormal cardiovascular structure

Eighty-five percent of heart muscle consists of type I collagen and OI patients tend to also have congenital heart disease¹³. The fragility of the cardiovascular structure

results in a lower tolerance for surgery. It is therefore necessary to assess such patients carefully before surgery.

Delayed wound healing

Abnormal type I collagen in OI cases makes them prone to delayed wound healing or disunion.

Progress in OI treatment

For fatal type II OI, the delivery schedule should be chosen individually based on the patient's and the mother's conditions. For the other types, in which the affected patients usually survive after birth, several methods have been reported to improve the patient's condition.

Bisphosphonates and estrogen

In current practice, several kinds of bisphosphonates are used to treat OI. Prescription of bisphosphonates for fetal OI should be limited to cases with multiple fractures, vertebral collapse and reduced bone content¹⁴. For older children, the indication should be a history of more than three fractures altogether, or more than two fractures within one year, combined with a T score < -2.0 by dual energy X-ray¹⁵. Clinical trials on infants and children have proved that bisphosphonates can dramatically increase vertebral bone content, the growth rate of the vertebrae and mobility^{16–18}. However, bisphosphonates have their own limitation in that they reduce bone turnover. A study of pamidronate in OI has reported a reduction of as much as 70% in bone growth rate at the end of a 5.5 year follow-up¹⁹. There is currently no consensus on the best duration of bisphosphonate therapy in OI cases.

Some other researchers have proposed that estrogen can be used to treat infant OI. Antoniazzi *et al.* reported the effect of estrogen and neridronate on 30 children with OI²⁰. They found that the combination of these two drugs produced superior results (in regard to bone content, growth rate, and fracture rate) compared with treatment with bisphosphonate alone and the children's pre-treatment condition. Multiple drug combination therapy is therefore a prospective direction for OI treatment.

Braces and surgery

Braces has limited effects in OI. They can only prevent worsening of existing abnormality²¹. For patients with severe scoliosis (>50°), surgical management can achieve a good result after puberty²¹. Additionally, Saldanha *et al.* applied external fixation to correct the abnormality in six OI cases (mean age, 14.7 years) and achieved good results²².

Agarwal and Joseph followed 44 special OI cases with repeated fractures between 1989 and 2003²³. Nine non-

unions were encountered in eight patients. They therefore considered that non-union was common in OI cases. Care should be taken to choose the correct fixation method in OI patients with fractures and surgical treatment is recommended when necessary. Surgery can restore the shape of long bones, but the functional recovery is limited because of abnormalities in the surrounding soft tissue.

Stem cell transplantation

Stem cell transplantation is a newly developed approach for the management of OI. Li *et al.* transplanted mouse bone marrow mesenchymal stem cells into the femoral cavities of OI mice²⁴. Those exogenous mesenchymal stem cells changed into osteoblast cells in the OI mice and improved bone growth²⁴. Vanleene *et al.* transplanted human fetal blood stem cells into OI fetal rats in the uterus²⁵. They also found these stem cells changed into osteoblasts, secreting osteocalcin and synthesizing type I collagen. The normal type I collagen dramatically reduced bone brittleness and increased mechanical strength. Based on the beneficial effect of human fetal blood stem cells on OI fetal rats, it can be expected that human fetal blood stem cells or other stem cells will have a bright future in the human fetus with OI. Though fetal stem cell transplantation has not been reported in clinical practice, Horwitz *et al.* reported bone marrow transplantation or bone marrow derived stem cells for OI patients^{26,27}. They found these methods achieved good clinical results even when in low concentrations. Thus it is appropriate to use stem transplantation in OI treatment.

References

1. Starr SR, Roberts TT, Fischer PR. Osteogenesis imperfecta: primary care. *Pediatr Rev*, 2010, 31: e54–e64.
2. Gerhard DS, Wagner L, Feingold EA, *et al.* The status, quality, and expansion of the NIH full-length cDNA project: the Mammalian Gene Collection (MGC). *Genome Res*, 2004, 14: 2121–2127.
3. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet*, 1979, 16: 101–116.
4. Bulas DI, Stern HJ, Rosenbaum KN, *et al.* Variable prenatal appearance of osteogenesis imperfecta. *J Ultrasound Med*, 1994, 13: 419–427.
5. Thompson EM. Non-invasive prenatal diagnosis of osteogenesis imperfecta. *Am J Med Genet*, 1993, 45: 201–206.
6. Munoz C, Filly RA, Golbus MS. Osteogenesis imperfecta type II: prenatal sonographic diagnosis. *Radiology*, 1990, 174: 181–185.
7. Ablin DS. Osteogenesis imperfecta: a review. *Can Assoc Radiol J*, 1998, 49: 110–123.

8. Wenstrup RJ, Willing MC, Starman BJ, *et al.* Distinct biochemical phenotypes predict clinical severity in nonlethal variants of osteogenesis imperfecta. *Am J Hum Genet*, 1990, 46: 975–982.
9. van Dijk FS, Huizer M, Kariminejad A, *et al.* Complete COL1A1 allele deletions in osteogenesis imperfecta. *Genet Med*, 2010, 12: 736–741.
10. Semler O, Cheung MS, Glorieux FH, *et al.* Wormian bones in osteogenesis imperfecta: correlation to clinical findings and genotype. *Am J Med Genet A*, 2010, 152A: 1681–1687.
11. Ghosh A, Woo JS, Wan CW, *et al.* Simple ultrasonic diagnosis of osteogenesis imperfecta type II in early second trimester. *Prenat Diagn*, 1984, 4: 235–240.
12. Edge G, Okafor B, Fennelly ME, *et al.* An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. *Eur J Anaesthesiol*, 1997, 14: 215–219.
13. Oakley I, Reece LP. Anesthetic implications for the patient with osteogenesis imperfecta. *AANA J*, 2010, 78: 47–53.
14. Bachrach LK, Ward LM. Clinical review 1: bisphosphonate use in childhood osteoporosis. *J Clin Endocrinol Metab*, 2009, 94: 400–409.
15. Shapiro JR, Sponseller PD. Osteogenesis imperfecta: questions and answers. *Curr Opin Pediatr*, 2009, 21: 709–716.
16. Antoniazzi F, Zamboni G, Lauriola S, *et al.* Early bisphosphonate treatment in infants with severe osteogenesis imperfecta. *J Pediatr*, 2006, 149: 174–179.
17. Munns CF, Rauch F, Travers R, *et al.* Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. *J Bone Miner Res*, 2005, 20: 1235–1243.
18. Glorieux FH. Treatment of osteogenesis imperfecta: who, why, what? *Horm Res*, 2007, 68 (Suppl. 5): S8–11.
19. Rauch F, Travers R, Glorieux FH. Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. *J Clin Endocrinol Metab*, 2006, 91: 511–516.
20. Antoniazzi F, Monti E, Venturi G, *et al.* GH in combination with bisphosphonate treatment in osteogenesis imperfecta. *Eur J Endocrinol*, 2010, 163: 479–487.
21. Song D, Maher CO. Spinal disorders associated with skeletal dysplasias and syndromes. *Neurosurg Clin N Am*, 2007, 18: 499–514.
22. Saldanha KA, Saleh M, Bell MJ, *et al.* Limb lengthening and correction of deformity in the lower limbs of children with osteogenesis imperfecta. *J Bone Joint Surg Br*, 2004, 86: 259–265.
23. Agarwal V, Joseph B. Non-union in osteogenesis imperfecta. *J Pediatr Orthop B*, 2005, 14: 451–455.
24. Li F, Wang X, Niyibizi C. Bone marrow stromal cells contribute to bone formation following infusion into femoral cavities of a mouse model of osteogenesis imperfecta. *Bone*, 2010, 47: 546–555.
25. Vanleene M, Saldanha Z, Cloyd KL, *et al.* Transplantation of human fetal blood stem cells in the osteogenesis imperfecta mouse leads to improvement in multi-scale tissue properties. *Blood*, 2011, 117: 1053–1060.
26. Horwitz EM, Gordon PL, Koo WK, *et al.* Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: implications for cell therapy of bone. *Proc Natl Acad Sci USA*, 2002, 99: 8932–8937.
27. Horwitz EM, Prockop DJ, Gordon PL, *et al.* Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. *Blood*, 2001, 97: 1227–1231.