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Osteogenesis Imperfecta: Primary Care

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Drs Starr, Roberts,
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Objectives After completing this article, readers should be able to:

1. List the types and clinical features of osteogenesis imperfecta (OI), including the potential overlap with abuse.
2. Recognize that deafness is associated with OI.
3. Identify common specific clinical issues and treatments for children who have OI.
4. Discuss additional issues that should be reviewed at health supervision visits for infants, young children, adolescents, and young adults who have OI.

Introduction

Osteogenesis imperfecta (OI), a heritable disorder, occurs in 1 in 10,000 to 15,000 liveborn children and affects people of all ethnicities. An estimated 25,000 to 50,000 individuals in the United States are born with OI. OI is the result of a genetically abnormal bone matrix that does not respond appropriately to mechanical loads, leading to an increase in osteoblast number and osteoclast activity, accelerated bone turnover, and high risk for fractures.

It is important for all general pediatricians to be familiar with OI to ensure early diagnosis and optimal health outcomes. Pediatricians should be prepared to coordinate health maintenance and provide a medical home for affected individuals until they can be transitioned successfully to adult clinicians during young adulthood. Sometimes pediatricians must differentiate OI from abuse and other conditions that can mimic OI.

Diagnosis

The diagnosis of OI may be based on clinical or biochemical analysis, depending on the clinician's degree of suspicion. Evaluation should involve exploring all aspects of family history, medical history (including gestational history), and physical examination. Special laboratory testing, guided by a geneticist, may be required if OI is suspected because not all patients can be diagnosed accurately based only on history, physical examination, and radiographic findings.

History and Physical Examination

In addition to findings obtained on routine neonatal history and physical examination, potential findings indicative of OI are noted in Table 1. Common findings include triangular facies, blue- or gray-tinted sclerae, chest deformities such as pectus excavatum or carinatum, and joint laxity. During physical examination, the clinician should palpate the skeleton for fractures, deformities, calluses, and areas of swelling, inflammation, or tenderness.

Radiographic and Laboratory Findings

Radiographic findings of OI include neonatal fractures; osteopenia; and deformities such as bowing, vertebral compressions (codfish vertebrae), and wormian bones (nonspecific findings of small irregular bones in skull sutures, seen in 60% of OI patients). To rule out other confounding conditions in children who have fractures, laboratory studies, including a complete blood count and serum mono- and divalent electrolyte concentrations, can be useful. Severely affected children may exhibit hypercalciuria. Alkaline phosphatase concen-

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Table 1. History and Physical Examination for an Infant With Suspected Osteogenesis Imperfecta (OI)

History

- **Pregnancy and birth history:**
 - Review intrauterine ultrasonographic findings for rib or long bone fractures or skeletal deformities in severe types of OI; these abnormalities may be detected as early as 15 to 20 weeks' gestation.
 - Review labor and delivery records for fractures, deformities, and respiratory complications at birth.
- **Neonatal and past medical history:**
 - Inquire about history of fracture, including circumstance and mechanism of injury and stage of development at time of injury; irritability, fussiness, and intractable crying are suggestive of fracture.
 - Review child's physical growth and developmental progress; infants born with OI may exhibit varying degrees of weakness and hypotonia, and severely affected patients may exhibit poor weight gain and growth due to poor feeding.
- **Family history:**
 - Is there an existing diagnosis of familial OI? If not, inquire about relatives who have histories of atraumatic fractures, unusually short stature, or easy bruisability.

Physical Examination

- **General:**
 - Inspect for obvious deformities or disproportions, including fractured, bowed, or disproportionately short arms, legs, or trunk in moderately to severely affected individuals; those who have milder types may have normal proportions and appearance.
 - Observe for reduced mobility of a particular extremity or abnormal posturing; gross motor development may be delayed because of hypotonia or fractures.
 - Monitor for characteristic low birthweight as well as disproportionately large head; severely affected (type II) individuals exhibit respiratory distress because of extremely small chests and statures.
- **Head, Ears, Eyes, Nose, and Throat:**
 - Inspect for abnormal facies, which are classically triangular in appearance; findings in severely affected individuals include hypoplastic mandibles, shallow orbits, small noses, and low nasal bridges.
 - Inspect sclera for blue or grey tint that persists beyond infancy, a finding that is typical of 50% of OI patients and varies with regard to OI type and severity; vision is normal.
 - Palpate the infant's head, which may be soft or bulging or have large fontanelles that close later than those of unaffected infants. (1)
 - Examine oral cavity for signs of dentinogenesis imperfecta, looking for hypoplastic, transparent, amber/brown-colored, carious, or late erupting teeth, findings that are typical of 50% of affected patients and vary with type.
- **Chest:**
 - Inspect chest for deformities such as pectus excavatum or carinatum; rib cages may be short or narrow.
 - Evaluate respiratory function in moderately to severely affected individuals; pneumonias occur at higher rates in OI populations.
 - Auscultate for aortic valve disease or mitral prolapse; congenital malformation rates parallel those of unaffected individuals.
- **Abdomen:**
 - Inspect and palpate for inguinal or umbilical hernias, which occur at higher rates than normal.
 - Evaluate for pelvic malformations, which may exacerbate constipation, a common complication of OI.
- **Extremities:**
 - Inspect and palpate skeleton for fractures, deformities, calluses, or areas of swelling, inflammation, or tenderness.
 - Passively test joint range of motion, which may be hyper- or hypomobile.
 - Hypomobility may result from active resistance caused by pain from fracture or from anatomic abnormalities such as bowing and callus formation.
 - Diminished ranges of pronation and supination, as well as hyperplastic callus formation, are characteristic of type V OI patients.
 - When evaluating infants for congenital hip dysplasia, consider ultrasonographic testing in lieu of Ortolani and Barlow maneuvers, which may induce fractures.
- **Back:**
 - Evaluate for obvious deformities, compression fractures, scoliosis, or kyphosis.
- **Skin:**
 - Palpate for unusually stiff skin with decreased elasticity; moderately to severely affected individuals may experience easy bruising because of capillary fragility.

trations may be elevated due to the presence of fractures in healthy children as well as children affected with OI.

In mildly affected patients, a clinical diagnosis of OI might be difficult. Testing cultured fibroblasts for the genes encoding collagen I (*COL1A1* and *COL1A2*) from a skin biopsy can pinpoint the diagnosis with 86% and 96% sensitivities, respectively. (2) A negative test result, however, does not preclude the diagnosis of OI because patients who have some OI types V through VIII do not have these mutations.

Pathogenesis and Types of OI

Historically, OI has been classified as types I through IV, based on clinical picture, inheritance patterns, and radiographic findings. Modern classification schema reframe these clinical types by their molecular origins, namely, mutations in the genes *COL1A1* and *COL1A2* and other related proteins, and expand the types to include several new forms, types V through VIII (Table 2). Because many patients still do not have discernable mutations, the new OI classification remains primarily clinical. The numbered designation of OI types is not related to increasing severity or prevalence.

Molecular Classifications

Collagen I, the predominant collagen of bone, teeth, tendons, and skin, consists of a triple helix from two fibrillar products of the *COL1A1* gene and one from *COL1A2*. Mutations in either gene (typically a glycine substitution causing disruption of the tightly wound helix) cause OI types II through IV, which are distinguished by clinical severity. Type I OI is the result of a more specific process: a *COL1A1* mutation codes a premature stop codon or “nonsense” mutation. These truncated products are destroyed by “nonsense-mediated decay” and, thus, only normal type I chains are produced. The result is a quantitative defect in collagen, resulting in a relatively mild clinical picture. Types II through IV, by contrast, are qualitative disorders of collagen because the aberrant product is incorporated into tissues.

Clinical Classifications

Type I OI is the most common and clinically mild form of the disease. Type II, by contrast, is comparatively rare and is the most severe form of OI, typically causing perinatal demise because of respiratory failure. Among patients who have OI and survive the newborn period, type III, which is relatively common, is the most severe form of OI. Affected patients experience progressive deformities and frequent fracturing as they develop and

typically become wheelchair-bound. Type IV, the most clinically diverse type of OI, presents with a wide range of severity and findings. Types I through IV are inherited in an autosomal dominant pattern.

“New” Types of Osteogenesis Imperfecta

The newly described types V through VIII do not result from mutations in genes encoding collagen I, and affected patients do not exhibit typical findings associated with OI such as tinted sclerae, hearing loss, or dentinogenesis imperfecta (DI). Type V, a former subset of IV, is characterized by a broad phenotypic range of mild-to-severe fragility and currently is not associated with a known gene mutation. Patients in this group may be distinguished by their tendency to develop hypertrophic calluses following trauma or surgery. Such calluses may be mistaken radiographically for osteosarcoma. In addition, type V patients tend to exhibit abnormally mineralized interosseous membranes, with secondary dislocation of radial heads and decreased forearm pronation and supination.

Type VI OI has a varied clinical picture of moderate-to-severe deformities characterized by a mineralization defect similar to osteomalacia. The molecular origins of type VI OI are unknown. Inheritance, unlike types I through V, is autosomal recessive.

Types VII and VIII OI are the most recently described types, resulting from respective mutations in *CRTAP* (cartilage-associated protein) and *LEPRE1* (prolyl 3-hydroxylase 1) genes. Inheritance of both diseases follows autosomal recessive patterns. Patients who have type VII disease exhibit moderate-to-severe deformities and fragility; type VIII disease is characterized by severe growth and mineralization deficiencies. Together, types VII and VIII account for fewer than 10% of OI patients.

Diagnosing the type of OI in a pediatric patient is especially relevant when discussing with parents the treatment goals, prognosis, and expectations for their child. For families facing a new diagnosis of OI, understanding this disorder’s pathogenesis and inheritance pattern is an essential part of genetic counseling.

Case 1: Newborn

An apparently healthy term newborn presents at 3 weeks of age with intractable crying and decreased mobility of her left leg. Her parents are unaware of any specific injury. On physical examination, the infant’s sclerae appear somewhat blue. Plain radiographs show a fracture at the proximal femoral metaphysis, and additional evaluation with a skeletal survey reveals several rib fractures.

Table 2. Classification of Osteogenesis Imperfecta by Molecular and Clinical Characteristics

Type	Genetic Mutation	Inheritance	Severity	Stature	Scoliosis	Sclera	Dentinogenesis Imperfecta	Hearing Loss	Specific Findings	Treatment Goals
I	Premature stop codon (nonsense mutation) in COL1A1	AD	Mild fragility, minimal deformity	Normal to slightly short	Minimal	Blue	Typically absent	50%	Often appear normal; may not fracture until ambulatory.	Maximize mobility and function, increase bone mass, develop strength. Early intervention with PT/OT. Frequent exercise and activity.
II	Glycine substitution in COL1A1 or COL1A2	AD	Lethal in perinatal stage, severe fragility and deformity	Severely reduced	Severe	Dark blue/gray	Not applicable	Not applicable	Very short limbs, small chest, soft skull with relatively large head. Multiple rib and long bone fractures in utero or in perinatal period. Very low-density skull bones on radiology. Patients often exhibit pulmonary hypoplasia and die due to cardiopulmonary complications.	Cardiopulmonary support. Assisted feeding for dysphagia. Patients typically die within weeks of delivery. Counsel family and provide genetic counseling. Early bisphosphonates therapy may be beneficial in few surviving cases. (3)
III	Glycine substitution in COL1A1 or COL1A2	AD	Moderate-to-severe fragility, severe deformity	Severely reduced; adults typically <3'6"	Severe	White/blue/purple/gray	Typically present	Frequent	Triangular facies with relatively large head. Mildly shortened and bowed limbs, small chest, and soft calvarium. Respiratory complications, dysphagia, and fractures are common in the perinatal period.	Fracture and deformity prevention efforts, including lifestyle/behavior modification, bracing, rodding, and monitoring for scoliosis. May require respiratory function monitoring, PT/OT for maximizing mobility and function and for assisted-living devices such as wheelchairs. Early bisphosphonate therapy.
IV	Glycine substitution in COL1A1 or COL1A2	AD	Broad phenotypic range of fragility and deformity	Moderately short	Mild-to-moderate	White/gray	Varied	Some	May not fracture until ambulatory. Short, mildly bowed humeri and femurs.	Fracture and deformity prevention as described above. PT/OT for maximizing mobility and function and for assisted-living devices such as wheelchairs. Early bisphosphonate therapy. Frequent exercise and activity.
V	Unknown	AD	Broad phenotypic range of fragility and deformity	Mild to moderately short	Variable	White	None	None	Hyperplastic callus formation in long bones, mineralization of interosseous membranes, dislocation of radial head and diminished wrist rotation.	Fracture and deformity prevention as described above. PT/OT for maximizing mobility and function and for assisted-living devices such as wheelchairs. Frequent exercise and activity.
VI	Unknown	Unknown	Moderate fragility and deformity	Moderately short	Unknown	White	None	None	Exceedingly rare. Fish-scale pattern on lamellation, accumulation of osteoid in bone tissue. Rhizomelic shortening (short proximal limbs).	Supportive treatments. PT/OT.
VII	Partial expression of CRTAP	AR	Moderate fragility and deformity	Moderately short	Moderate	White	None	None	Rhizomelic shortening with coxa vara. May resemble type II patients with small head and round face.	Supportive treatments. PT/OT.
VIII	Mutation in LEPRE1	AR	Severe fragility and deformities	Severely reduced	Severe	White	Unknown	Unknown	Severe growth deficiency. May resemble type II or III patients. Extreme undermineralization of skeleton.	Supportive treatments. PT/OT.

AD=autosomal dominant, AR=autosomal recessive, COL1A1, COL1A2=genes that encode collagen I, CRTAP=cartilage-associated protein gene, LEPRE1=prolyl 3-hydroxylase I gene, OT=occupational therapy, PT=physical therapy
Adapted from Glorieux.(4)

Fractures in early infancy evoke a broad and sobering differential diagnosis, ranging from nonaccidental trauma to hereditary connective tissue disorders. If OI is diagnosed, parents require detailed counseling on the special needs of their child. The pediatrician should begin coordinating the infant's care using a multidisciplinary team.

Evaluating the Child Who Has Isolated Blue Sclerae

The presence of blue sclerae is highly suggestive but not an expressly diagnostic feature of some OI types. Its differential diagnosis includes various other connective tissue diseases such as Ehlers-Danlos and Marfan syndromes and nutritional disorders such as iron-deficiency anemia. Otherwise healthy infants who have idiopathic thinned sclerae may exhibit sclerae with a pale blue hue, a normal finding until 18 months of age. (1) Intensely darkened or gray sclerae persisting beyond 2 years of age should be evaluated.

Evaluating the Infant Who Has Multiple Fractures

The presentation of unexplained fractures in a child necessitates evaluation for physical abuse. Some estimate that a child is 24 times more likely to have broken bones from nonaccidental trauma than from OI. (5) Although abuse may result in any form of fracture, metaphyseal, posterior rib, and skull fractures are among the most common. These are the same types of fractures seen in OI. Beyond nonaccidental trauma and OI, potential causes of multiple fractures in older infants include other connective tissue disorders; metabolic disorders such as hypophosphatasia and juvenile Paget disease; endocrine abnormalities such as Cushing disease or chronic renal disease; and nutritional and environmental factors such as insufficient intake or metabolism of vitamins D or C, calcium, and copper. Fractures and bowing may occur later in the first postnatal year in cases of rickets due to isolated or combined deficiencies of calcium and vitamin D. Preterm infants may exhibit osteopenia in their first postnatal year (osteopenia of prematurity) because of insufficient mineral intake during fetal life. Early osteomyelitis, especially in infants who have fever, may present as multiple lesions at the metaphyses of long bones and may be mistaken for abuse.

Caring for the Newborn Who Has OI

Even before the ride home from the hospital, parents must give special care to children born with OI. Although standard, well-padded car seats with lateral head

support pillows are recommended, they should be used only when the infant can tolerate sitting upright. Once home, parents may use a standard crib mattress. To prevent cranial deformity, infants should be placed on their sides with frequent position changes. Parents should use a gel pad for the head if the crib mattress is firm.

For healthy bone and motor development, all children require physical activity and stress. Children born with OI should be allowed to engage in gradual, carefully monitored physical activity. Bath time, for example, allows children to move in a near-weightless but resistant environment. Caregivers should avoid pushing, pulling, twisting, or lifting the infant by the extremities as well as lifting the infant from under the axillae. Instead, when lifting the child, caregivers should place one hand behind the head while the other hand supports the trunk and buttocks. During diaper changes, caregivers should lift the infant under the buttocks with a free hand rather than lift the infant's ankles or feet. The goal for physically handling an infant or child is even and wide distribution of pressure on the fragile body. Infants who have OI should not be patted on the back, as is typically recommended for burping. All but the most severely affected infants should be able to breastfeed.

Following a new diagnosis of OI, parents may experience exacerbated postpartum "blues" or depression, may harbor a sense of guilt, and sometimes may bear expensive medical bills. Physicians should be conscious of these factors, taking time to discuss the prognosis and treatment plans with families. It might be helpful to provide the family with a letter stating the diagnosis to avoid unnecessary concern by other caregivers for abuse. Pediatricians also can direct parents to resources such as the Osteogenesis Imperfecta Foundation's website (www.oif.org) and the National Institutes of Health (NIH) (www.niams.nih.gov/bone). Parents of children born with OI often benefit from contact with other parents who have similarly affected children. (6)

Case 2: Child

A recently relocated 18-month-old girl who has OI presents for a health supervision visit. She has a history of multiple fractures and was followed by a multidisciplinary team (orthopedic surgery, endocrinology, physiatry, physical therapy) at her previous medical center. In addition to getting her daughter established with a new health-care team, the mother is wondering what special care is necessary at this time.

The physician should review long-term goals in caring for patients who have OI. Major goals include minimizing the risk of mortality and improving the quality of life.

Pediatricians should work as members of a team consisting of the child, the parents, and other health-care professionals to minimize pain, maximize mobility, and enable the child to lead a social and academic life that is as fulfilling as those of his or her peers. As with other children who have complex chronic health conditions, children who have OI need a consistent medical home that has a primary care clinician and a team to orchestrate longitudinal care.

Routine Health Maintenance for Children Who Have OI

The NIH, in cooperation with the Osteogenesis Imperfecta Foundation guidelines published in 2007, summarizes the diagnosis, management, and resources for primary care clinicians. (1) Table 3 summarizes special issues, interventions, and referrals that should be addressed at health supervision visits for infants, children, and adolescents who have OI.

Table 3. Special Considerations at Health Supervision Visits for Children Who Have OI

All Ages

- History
 - Assess pain
 - Assess quality of sleep
 - Assess toileting concerns, especially constipation
 - Assess level of physical activity and exercise
 - Assess family coping and financial impact of child's chronic illness
- Physical Examination
 - Screen for kyphoscoliosis
- Interventions
 - Consider 23-valent pneumococcal vaccine after 2 years of age if there is respiratory compromise or restrictive lung disease
 - Provide tailored anticipatory guidance regarding modification of home environment given small stature, injury prevention, appropriate car safety restraint, and ways to minimize respiratory infections
- Referrals
 - Pediatric physiatrist, physical therapy, and occupational therapy to help develop plan for ambulation (in severe forms of OI) and to provide a comprehensive approach for safe physical activity to maximize mobility and function and increase peak bone mass and muscle strength (all children who have OI)
 - Orthopedic surgeon for ongoing management of skeletal deformities, assessment of scoliosis, and (in severe forms) potential rod placement if lower extremities are bowed to assist with ambulation
 - Social worker for issues related to financial concerns and difficulties with family coping

Infancy

- Referrals
 - Genetics consultation to confirm diagnosis and provide genetic counseling
 - Pediatric endocrinology consultation regarding early bisphosphonate therapy
 - Early intervention services via the county after severe OI is diagnosed or at first sign of delay
 - First dental visit at 1 year of age to evaluate for dentogenesis imperfecta

School Age and Adolescent

- History
 - Ask about symptoms suggestive of basilar invagination (headache, dysphagia, dysphonia)
 - Assess child's or teen's strategies and success in terms of coping skills associated with stamina, social interactions, and overall quality of life
 - Screen for adverse effects if taking chronic medications for pain
 - Screen for mood disorder (anxiety, depression)
- Referrals
 - Audiogram at age 10 and every 3 years thereafter (7)
 - Pulmonary function testing if there are any concerns for respiratory difficulties or significant kyphoscoliosis

Nutrition and Growth

Children born with severe forms of OI may have low birthweights. Some patients exhibit slow growth; others have relatively large head circumferences. Young children may have delayed fontanelle closure. (1) Longitudinal growth may be limited. Torsos of children who have OI may appear shorter and barrel-shaped due, in part, to vertebral compression. Older children and adolescents should be monitored for increases in weight percentiles because obesity may increase morbidity by further increasing fracture risk. Pediatricians should ensure that children who have OI meet routine calcium and vitamin D intake recommendations.

Hearing

Hearing loss can occur in children who have OI. Commonly, the loss is conductive on presentation but evolves to a sensorineural or mixed loss. The pathophysiology is suspected to originate in disorganized, abnormally formed ossicles as well as from avascular fibrotic resorption in the ossicular bone matrix. (7) Traditionally, hearing loss in OI was believed to be uncommon before the age of 20, with approximately 50% of all adults who have OI and are older than 50 years of age having self-reported hearing loss. However, in two recent population-based Finnish studies, conductive hearing loss not attributable to otitis media with effusion was identified in 9% of all children (defined as <20 years of age) and 58% of all adults who had OI. The frequency and severity of hearing loss was not correlated with other clinical features of OI. Other investigators also have demonstrated hearing loss in children who have OI. (8) Tinnitus also is reported frequently in adults. Based on existing evidence, some experts suggest obtaining a baseline audiogram at 10 years of age and every 3 years thereafter. It is important to note that audiometric changes were noted before hearing loss was reported clinically in one study. (7) Early detection may enable treatment with middle ear surgery and hearing aid(s).

Immunizations

Individuals who have OI should receive all routinely recommended immunizations, including influenza vaccination beginning at 6 months of age. Children older than 2 years of age who have even mild respiratory compromise should receive the 23-valent pneumococcal vaccine.

Dentition

DI occurs in approximately 50% of patients who have OI (predominantly types III and IV) and is a result of the

same *COL1A1* and *COL1A2* gene mutations. DI is characterized by translucent, discolored (usually amber), brittle teeth and typically is more evident in primary teeth than in permanent teeth. DI does not affect children who have developed normal primary teeth. (1) Patients who have DI have abnormal dentine that is weak and wears rapidly, leading to root exposure that may become a source of infection and pain. Radiographic findings include teeth that have short, constricted roots and dentine hypertrophy. Treatment predominantly is supportive: removing sources of infection or pain, protecting teeth from wear, and restoring esthetics in older individuals. Early instruction for parents on good dental hygiene and referral to dental professionals is essential in addition to routine dental care.

Motor Development

Children born with OI have normal cognition despite possible gross and fine motor delays. Motor delays can occur from recurrent fractures, postfracture deformity, fracture-related immobilization, and hypotonia. Self-care deficits might prompt the need for assistance with ambulation, toileting, and transferring. Children who have OI may require support in school for these difficulties as well as other adaptations (such as voice recognition software). Families have identified unique housing needs (such as locating the bedroom of the child nearest to the bathroom) as a very important issue that may not be addressed routinely in the context of health supervision visits. (6)

Physical activity programs help to prevent contractures, minimize risks for fractures, and minimize bone loss from immobilization. Children born with type I OI have reduced exercise capacity due to proximal muscle weakness and reduced peak oxygen consumption, although aerobic capacity improves with structured exercise programs. (9) Almost all patients who have OI benefit from physical and occupational therapy. Pediatric physiatrists and physical therapists are important members of the OI care team, and early referral is advised. These specialists are vital in helping children who have OI minimize risks for fractures and maximize the likelihood for autonomous or, at least, assisted ambulation. They also can assist patients and parents in learning safe techniques for lifting, sitting, and standing for children of all ages. Standing and walking are supported early in life via assist devices, but ambulation may not be achieved in moderately-to-severely affected individuals until they have telescoping intramedullary rods inserted in their femurs and tibiae to straighten and support these long bones.

Early intervention programs provide effective, accessible pediatric physical and occupational therapy, and American school districts can facilitate care for children 3 years of age and older. These community resources play a key role in the functional success of children who have OI, and their involvement should be integrated with the efforts of the multidisciplinary medical team. School-age children who have OI and live in the United States may meet criteria for individualized education plans.

Sleep

When pediatricians screen for sleep problems during health supervision visits, they should ask parents about the quality of the child's sleep. Children who have significant orthopedic deformities with or without restrictive lung disease may experience hypoventilation in addition to poor sleep from pain or difficulty with comfortable transitioning.

Constipation

Children who have OI may be constipated because of pain medications, severe scoliosis, or pelvic malformation. In addition, limited mobility or reliance on others for transferring to the toilet or bedside commode can complicate both toilet training and independent toileting. A high-fiber diet from an early age may help children who have OI minimize constipation.

Bone Health

Injury prevention takes on a new level of meaning in children who have OI. For those whose OI is moderate to severe, some experts recommend measuring blood pressures manually to decrease the risk of fractures from automated blood pressure machines, which may generate higher pressures compared with manual sphygmomanometers. Pediatricians should work with parents to identify ways to decrease falls and potential injuries. Children who have OI may benefit from a well-padded car seat harness and a support pillow that "hugs" the head. Consultation with clinicians who have expertise in child passenger safety can be arranged, and some hospitals or local charitable organizations such as Easter Seals may loan car seats to children who are in spica casts for treatment of fractures. (1)

Intravenous bisphosphonates such as pamidronate decrease chronic bone pain and increase vertebral bone mineral mass and mobility. These drugs inhibit osteoclast function, thereby decreasing bone resorption. Because bone formation is abnormal in patients who have OI, however, bisphosphonates do not offer a cure. It is

unknown if intravenous bisphosphonates prevent long bone deformities or the progression of scoliosis. At this time, the comparative efficacy of oral versus intravenous bisphosphonates is unclear. Some evidence from multiple small studies suggests that bisphosphonate therapy administered as early as several weeks of age to severely affected neonates may increase bone mineral density and reduce rates of fracture. (3) Early treatment also may prevent scoliosis and basilar invagination. (10) Basilar invagination occurs when the occipital bone softens in conjunction with repetitive minor trauma. Such softening can cause elevation of the clivus and the posterior cranial fossa, leading to superior migration of the dens of the axis into the foramen magnum.

Jaw necrosis has been reported in older people receiving bisphosphonate therapy. Some authors recommend holding bisphosphonate therapy for 4 to 6 months following orthopedic surgery and assessing healing by radiographs before resuming treatments. Clinical severity, rather than bone mineral densitometry, guides treatment with bisphosphonates; use in children who have milder forms of OI is controversial. When treating females of childbearing age, clinicians should bear in mind that bisphosphonates might persist in bone tissue for years after treatment. Of note, the United States Food and Drug Administration has not approved bisphosphonate use for treatment of OI.

Other proposed medical therapies, such as growth and parathyroid hormones as well as bone marrow transplantation, are not used commonly in children because of insufficient evidence for efficacy and concerns for safety.

Surgical procedures can decrease the lifetime risk of deformity while increasing function in children who have OI. Indications for surgical realignment and placement of intramedullary rods include recurrent fractures, nonhealing fractures, and severe bowing in the lower extremities in children attempting to stand.

All children born with OI should be screened regularly for kyphosis and scoliosis. Scoliosis involving a greater than 30-degree curve occurs in 100% of children who have type III OI. Indications for surgical correction include curvature of more than 45 degrees in children who have mild OI or more than 30 to 35 degrees for severely affected individuals. Surgical intervention in children who have types III and IV OI may occur earlier (7 to 8 years of age) than in nonaffected children who have scoliosis because of limited trunk growth. Postoperative muscle spasms can be relieved with short-term diazepam.

Acute Fracture Management

When a fracture is suspected, caretakers first should splint the injury to minimize discomfort. Emergent care may be sought in cases of new deformity or severe pain. The primary clinician should work closely with the orthopedic surgeon to determine when radiographs are needed to help manage acute fractures and maximize long-term outcomes. Not all bone pain requires radiography; the decision not to image bone pain should be left to the orthopedist. For mildly affected patients who are bisphosphonate-naïve, bone healing typically occurs at normal rates.

Pain Management

Pain frequently is undertreated in children who have OI. In addition to pain from fractures, there are anecdotal reports of chronic musculoskeletal pain and headaches caused by basilar invagination. Both acute and chronic pain frequently interfere with daily activities and quality of life; pharmacologic therapy can help improve function.

Case #3: Adolescent

A 16-year-old boy born with a severe form of OI presents to his long-term pediatrician to address multiple health concerns. Previously a top student who was active in many extracurricular and physical activities, he has missed most school days in the past several years. His parents provide most of his daily care and are concerned about his ability to complete high school.

When caring for severely affected children and teens who have OI, it may be most important for pediatricians to review shared long-term health goals frequently. Pediatricians should use a holistic, patient- and family-centered approach in their efforts to minimize risks for mortality and improve quality of life.

Mortality and Morbidity

Individuals who have mild and moderate forms of OI have normal life expectancies. Causes of mortality in patients born with severe OI (not including type II, which is fatal in the neonatal period) include death from respiratory events, cardiovascular failure (due to severe kyphoscoliosis), neurologic sequelae, and cranial trauma that causes intracranial hemorrhage. In one study describing traumatic causes of death in OI patients, the most common reasons for traumatic death were motor vehicle crashes and falls from a wheelchair when unstrapped. (11) Neurologic causes are less common and include compression of the brainstem from basilar invagination.

Morbidity is significant in children who have severe forms of OI and includes immobility, lack of ambulation (either due to acute fractures or inability to walk long-term), orthopedic deformities contributing to restrictive lung disease, basilar invagination, acute and chronic pain, dental problems, hearing loss, respiratory compromise, poor sleep with or without hypoventilation, academic underachievement, social isolation, dependence on caregivers for activities of daily living, and secondary mood changes. As with all chronic diseases of childhood, parents and siblings of these children also may be affected adversely. Pediatricians can facilitate support for these family members.

Chronic Pain Management

A comprehensive approach for any child who has chronic pain is important and includes assessing pain at every visit, maximizing nonpharmacologic methods to manage pain, discussing appropriate use of analgesics, and monitoring for potential adverse effects of such medications. Local specialists such as pediatric anesthesiologists who have additional training in pain management as well as pediatric pharmacists can assist OI patients and their parents. Bisphosphonate therapy has been shown to help decrease pain.

Children and adolescents who require intermittent or chronic narcotic analgesia should be monitored carefully for adverse effects such as constipation, sedation, itching, and dependence. Because children born with OI are predisposed to constipation, clinicians should be proactive in minimizing any pain with defecation as well as preventing straining with its potential for causing fractures. A high-fiber diet, stool-softening agents, and laxatives may be required. In addition, the pediatrician should work closely with the patient's school to ensure that he or she has appropriate access to both narcotic and non-narcotic pain medications. Teens requiring chronic narcotic medications may benefit from comprehensive outpatient pain rehabilitation programs that maximize coping strategies while minimizing the effects of chronic pain on daily function.

Respiratory Considerations

Severely affected infants born with OI may have upper airway obstruction requiring tracheostomy. Those who have OI, like other individuals who have kyphoscoliosis or chest wall deformities, have an increased risk of restrictive lung disease. Patients should be immunized to decrease the incidence of respiratory infection. Children and adolescents who have OI should be evaluated promptly when presenting with respiratory signs and

fever, and antibiotic therapy should be considered. Patients also may benefit from incentive spirometry to minimize the risk of lower respiratory tract infection.

Neurologic Considerations

Intracranial hemorrhage from trauma, hydrocephalus, basilar invagination, and sleep disturbances comprise many of the neurologic sequelae of OI. In a retrospective NIH study of 76 patients born with OI, 13% had macrocephaly, seen most frequently in those who had type III disease. The macrocephaly sometimes was due to subdural hematomas. Twenty percent of the OI children had basilar invagination and spinal fractures.

Basilar invagination may present with headaches, lower cranial nerve abnormalities, dysphagia, respiratory compromise, weakness, and ataxia. Basilar invagination is a potentially fatal complication. Treatment is controversial and includes external occipitocervical bracing and ventral surgical decompression with and without dorsal stabilization. Progression of basilar invagination occurred following ventral decompression alone in one study. (12) The natural progression of this condition varies, and routine repeated imaging studies of asymptomatic children who have OI is not recommended.

Children and teens who have severe forms of OI may have significantly disrupted sleep. Disrupted sleep is multifactorial; origins include poor sleep from pain, difficulty with safe or comfortable positioning in cases of significant skeletal deformity, hypoventilation due to brainstem changes, poor ventilation caused by restrictive lung disease, obstructive sleep apnea, and mood disorders.

Other Findings

Abnormal bleeding and easy bruising in OI patients is due to vessel fragility and platelet dysfunction, decreased platelet retention, and reduced factor VIII R:Ag. (1) (12) Aortic and vertebral artery dissections, carotid-cavernous fistulas, cervical artery dissections, ulnar artery aneurysms, and moyamoya-type presentations have been reported. OI patients appear to be at increased risk for aortic root dilatation and mitral valve prolapse. Patients who have OI commonly have joint laxity, and hernias and myopia are more frequent than in the general population. Hypercalciuria and nephrolithiasis are not uncommon. (1) Perioperative hyperthermia that differs from true malignant hyperthermia has been reported.

Achieving Academic and Social Success

Adolescents who have severe OI face the same challenges common to all patients who have chronic disease. During normal adolescence, teens begin to shape their identities,

identify more with their peers, and seek independence from their parents. Adolescents who have OI can encounter obstacles in this transition to adulthood. Issues related to body image and sexuality may be difficult because of physical limitations and deformities. These challenges can be compounded when adolescents who have OI experience a delay in academic progress and achievement toward their life goals. Pediatricians who are skilled in individualizing an overall “big picture” plan for these teens and their families can affect outcomes favorably.

The normal progression of the relationship among pediatrician, adolescent patient, and parents may be disrupted because of the teen’s significant reliance on his or her parents for daily activities. Even parents who are deliberate in including the child’s voice in ongoing care may find it difficult to facilitate the patient’s transition to autonomous adulthood and the ability to navigate the health-care system independently. Parents have spent years being protective and may have difficulty enabling the young adult to have developmentally appropriate freedom and autonomy. Pediatricians of young adults who have OI can help to identify a new medical home and subspecialty contacts as these patients transition to adult clinicians. Young adults who have OI should be encouraged to use resources available on the Osteogenesis Imperfecta Foundation website.

Summary

- OI is an uncommon genetic disorder that requires longitudinal care coordinated by pediatricians in a well-organized medical home. From the first moments in a child’s life, pediatricians may be called on to differentiate OI from nonaccidental trauma and other conditions that lead to multiple fractures in infants.
- Based on some research experience, health supervision visits for children who have OI should include evaluation for pain, sleep, functional outcomes (academic and social success), referrals to other multidisciplinary team members, strategies for life-long physical activity, early identification of hearing loss, and smooth transition to practitioners experienced in managing adults who have OI.
- Based on some research evidence, patients born with OI should have their first audiogram by age 10 years and every 3 years thereafter. (7)
- Based on one study and anecdotal evidence, it is important for parents and families of children born with OI to identify a pediatrician who offers time, listens to parents’ experiences and needs, tries to understand, and shows empathy. (6)

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Resource for Patients, Parents, Teachers, and Health Care Clinicians

The Osteogenesis Imperfecta Foundation website (www.oif.org) includes resources for children, adolescents, parents, and educators as well as links to online support groups.

Osteogenesis Imperfecta: Primary Care
Stephanie R. Starr, Timothy T. Roberts and Philip R. Fischer
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